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WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

November 1, 2006

MEMORANDUM

SUBJECT: **Aldicarb** (List A Case 0140, Chemical ID No. 098301). HED Revised Human Health Risk Assessment for the Reregistration Eligibility Decision Document (RED). DP Barcode No. D331540.

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Attached is a revised human health risk assessment for aldicarb prepared by Reregistration Branch 1 (RRB1) of the Health Effects Division. This document has been revised to incorporate comments received during the public comment period. A response to comments document was also prepared which summarizes and illustrates specifically how the comments were addressed for the risk assessment. This document is entitled "**Aldicarb** (List A Case 0140, Chemical ID No. 098301). HED Response to Comments Received During the Public Comment Period. DP Barcode No. D331538."

The aldicarb risk assessment team is comprised of Felecia Fort (risk assessment, and dietary exposure assessment); Christina Swartz (residue chemistry chapter,); Linda Taylor (hazard assessment), Jeff Dawson (occupational risk assessment), all of HED and Jonathan Angier and Nelson Thurman of EFED (drinking water estimates).

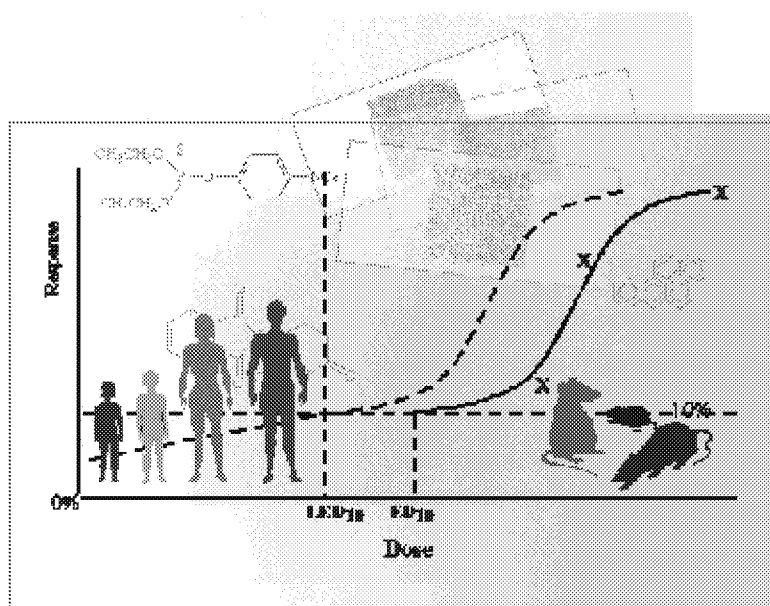
An intentional dosing human oral study [Inveresk] was relied upon in this risk assessment. This study has been reviewed by EPA's Human Studies Review Board (HSRB), as required by EPA's

Human Subjects Protections Rule (40 CFR part 26 (effective April 7, 2006)). The HSRB discussed the study extensively during a meeting held on April 2-4, 2006 and concluded that the cholinesterase data from the aldicarb human study were reliable for use in the aldicarb single chemical, aggregate risk assessment. Additionally, it was concluded that there was no clear and convincing evidence of significant deficiencies in the ethical procedures that could have resulted in serious harm (based on the knowledge available at the time the study was conducted), nor that information provided to participants seriously impaired their informed consent. The final report of the HSRB is available at <http://www.epa.gov/osa/hsrb/files/april2006mtgfinalreport62606.pdf>

Note to Risk Manager: Updated pesticide residue monitoring data from the USDA Pesticide Data Program (PDP) have not been incorporated into the dietary exposure assessment. However, the monitoring data support the results of the current assessment, and these data are not expected to result in any significant changes in estimated dietary exposure. It should also be noted that this assessment supercedes the previous occupational and residential exposure (ORE) assessment (D311821; January 11, 2005; Author: Jeff Dawson) and Toxicology RED chapter (D266321; August 20, 2002; Author: Linda Taylor, Ph.D). These chapters were not revised and reissued; instead, certain relevant modifications were included in this document.

HUMAN HEALTH RISK ASSESSMENT

Aldicarb



U.S. Environmental Protection Agency
Office of Pesticide Programs
Health Effects Division (7509C)
Felecia Fort, Chemist/Risk Assessor
Date: October 31, 2006

HUMAN HEALTH RISK ASSESSMENT

Aldicarb

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TABLE OF CONTENTS

1.0	EXECUTIVE SUMMARY.....	7
2.0	PHYSICAL/CHEMICAL PROPERTIES	16
3.0	HAZARD ASSESSMENT.....	16
3.1	Hazard Profile	16
3.2	Dose Response Assessment.....	21
3.2.1	Benchmark Dose (BMD) Analysis.....	21
3.2.2	Endpoint Selection	22
3.3	Reversibility.....	25
3.4	FQPA Considerations.....	26
3.5	Endocrine Disruption	27
4.0	EXPOSURE ASSESSMENT AND CHARACTERIZATION	27
4.1	Summary of Registered Uses	27
4.2	Dietary Exposure/Risk Pathway.....	28
4.2.1	Residue Profile	28
4.2.2	Dietary Exposure.....	30
4.2.2.1	Acute Dietary Exposure.....	32
4.2.2.2	Chronic Dietary	33
4.3	Water Exposure/Risk Pathway.....	35
4.3.1	Environmental Fate Properties	35
4.3.2	Estimated Environmental Concentrations (EECs)	36
4.4	Residential Exposure/Risk Pathway.....	38
5.0	AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATIONS ..	39
5.1	Acute Aggregate Risk Assessment [Food plus Drinking Water from Surface Water Sources] ..	40
5.2	Acute Aggregate Risk Assessment [Food plus Drinking Water from Ground Water Sources].	41
5.3	Chronic Aggregate Risk Assessment.....	44
6.0	CUMULATIVE RISK	44

7.0	OCCUPATIONAL EXPOSURE.....	45
7.1	Handler	46
7.2.	Incident Data	51
8.0	DATA NEEDS/LABEL REQUIREMENTS	52
8.1	Toxicology.....	52
8.2	Residue Chemistry	53
9.0	SUPPORTING DOCUMENTATION.....	53

1.0 EXECUTIVE SUMMARY

The Health Effects Division (HED) of EPA's Office of Pesticide Programs has evaluated the toxicity and exposure databases for the pesticide active ingredient aldicarb, and has conducted a human health risk assessment to support the reregistration of products containing aldicarb. This risk assessment addresses risks to aldicarb alone, and does not consider cumulative effects of other carbamate pesticides.

Use and Usage Information

Aldicarb is registered for use as a systemic insecticide, acaricide and nematocide on agricultural crops including citrus, cotton, dry beans, peanuts, pecans, potatoes, sorghum, soybeans, sugar beets, sugarcane, sweet potatoes, and seed alfalfa (CA). In addition, aldicarb may be applied to field grown ornamentals (CA) and tobacco, and on coffee grown in Puerto Rico. Pests controlled by aldicarb include leaf phylloxera; bud moth; citrus nematode (suppression); aphids; mites; white flies; thrips; fleahoppers, leafminers; leafhoppers; overwintering boll weevil; lygus; nematodes (suppression); cotton leaf perforator; seedcorn maggot; Mexican bean beetle; flea beetles; Colorado potato beetle; greenbug; chinch bug; three cornered alfalfa hopper (suppression); and sugar beet root maggot.

Aldicarb is a restricted use pesticide, and may only be applied in occupational settings by certified applicators. There are no aldicarb products intended for sale to homeowners or for use in residential settings. Aldicarb is formulated and marketed solely as a granular pesticide under the trade name Temik®. The granulars (5, 10 and 15%) consist of aldicarb adhered to a corn cob grit or gypsum substrate, which are formulated to produce less dust than typical clay substrates used for granular pesticides. The gypsum granular only is available in closed loading systems. Aldicarb is applied early in the growing season, either pre-plant, at-planting, or early post-emergent, using ground application equipment. Positive displacement application equipment and immediate soil incorporation are required.

Regulatory Background

Aldicarb is currently under Special Review because of concerns regarding ground water contamination. Position Documents (PD's) 1 and 2/3 were published on 7/11/84 (49 FR 28320) and 6/29/88 (53 FR 24630), respectively. A Special Review Data Call-In-Notice (DCI) was issued 6/3/89 requiring the registrant to submit additional ground water data. In addition, because a National Food Survey identified discrepancies between anticipated residues in foods and actual residues from food survey samples, the Special Review required a variety of studies related to use on potatoes and citrus crops. In 1990, the sale and use of aldicarb on potatoes were voluntarily suspended due to detection of tolerance-exceeding aldicarb residues on individual potatoes. Additional studies were conducted to alleviate concerns for dietary risk due to high residues in potatoes, and the use was reinstated in the states of FL, ID, WA and OR (EPA Desk Statement, 9/22/95). Aldicarb remains in EPA's Special Review process because of continued concerns about ground water contamination. A PD4 is to be issued in conjunction with a reregistration eligibility decision. Registrations of aldicarb currently reside with Bayer CropScience LP.

Hazard Profile and Food Quality Protection Act (FQPA) Decision

Aldicarb is an N-methyl carbamate pesticide that exerts its pesticidal activity and elicits adverse toxic effects by inhibition of cholinesterase activity [ChEI]. Overall, the studies supporting the toxicity database for aldicarb are considered adequate, and there is confidence in the hazard and dose response assessments. Acutely, aldicarb is highly toxic *via* the oral, dermal, and inhalation routes of exposure (Toxicity Category 1). It is not a dermal sensitizer; dermal and eye irritation studies were waived due to severe effects (death) following corneal and dermal dosing.

The toxicity database for aldicarb is adequate, including acceptable studies submitted to determine toxic effects associated with acute, subchronic and chronic exposure durations by the oral route; acceptable acute and subchronic neurotoxicity studies; a developmental neurotoxicity study in rats; developmental studies (rat and rabbit); and a reproduction study (rat). Acceptable dermal and inhalation toxicity and dermal penetration studies are not available.

Aldicarb toxicity studies have demonstrated inhibition of cholinesterase activity in whole blood, plasma, red blood cells (RBC) and brain of rats, mice, and dogs following acute, subchronic, and chronic exposures and in plasma and RBC in humans following acute exposure. It should be noted that aldicarb-induced ChEI has been shown to be reversible in less than 24 hours. Both the acute and subchronic rat neurotoxicity studies show a variety of typical clinical signs of ChEI after oral exposures to aldicarb, including decreased motor activity, lacrimation, tremors, salivation, pinpoint pupils, and decreased grip strength.

In guideline developmental or reproduction studies including a rat developmental neurotoxicity study submitted by the registrant, there was no indication of qualitative or quantitative susceptibility of offspring. Maternal toxicity occurred at doses where no offspring toxicity was observed; i.e., the no observed adverse effects level (NOAEL) for maternal toxicity was lower than the offspring NOAEL. A published non-guideline oral acute neurotoxicity study conducted by EPA/ORD (Moser) reported evidence for increased sensitivity of young rats based on brain ChEI measurements. Decreased motor activity was observed only in the adult animals, and clinical signs of ChEI occurred more frequently in, and recovery was more prolonged in the adult relative to the young animal. The magnitude of the brain ChEI was approximately 2-fold greater in the young rat compared to the adult rat at comparable acute doses. Therefore, a FQPA safety factor of 2X is retained.

In an acute oral study conducted in human volunteers, aldicarb treatment of both males and females resulted in statistically-significant inhibition of both red blood cell and plasma cholinesterase at two common dose levels. The results of the acute oral human study suggest a two-fold difference between animals and humans with respect to toxic responses following acute exposure to aldicarb, with humans being the more sensitive species.

The metabolism of aldicarb is well understood in animals (livestock and rats), plants, and in the environment (soil and water). In rats, with oral administration, aldicarb is rapidly absorbed, widely distributed, and rapidly eliminated. In rats, livestock, plants, and in the environment,

aldicarb is rapidly metabolized to aldicarb sulfoxide, then slowly converted to aldicarb sulfone. These three moieties (aldicarb, sulfoxide, and sulfone) may then be further metabolized to oximes and nitriles. Both the sulfoxide and sulfone are also potent cholinesterase inhibitors. The sulfone is less toxic following an acute oral exposure than either the parent compound or the sulfoxide, which show comparable acute oral toxicity. Aldicarb and its two cholinesterase-inhibiting metabolites are the residues of concern for risk assessment for all routes of exposure and for tolerance reassessment.

There are acceptable genotoxicity studies for all three required categories of mutagenic effects: gene mutations, chromosomal aberrations, and other genotoxic effects. The results of these studies are all negative. Aldicarb is not considered a mutagen, and it is classified as Category E, Evidence of Non-Carcinogenicity for Humans, based on the lack of evidence of carcinogenicity in studies in rats and mice.

Consideration of all available toxicity data was used to determine the toxicity endpoints and reference doses appropriate for the aldicarb risk assessment. There is a complete toxicology database of oral studies including a human oral study. HED's previous risk assessment reported risks using multiple endpoints, including those from the human study, to fully characterize risks, but focused on results using the rat RBC cholinesterase inhibition endpoint. This decision reflected the Agency's interpretation of the conclusions drawn by the HSRB prior to issuance of the final report. Based on the final report, which clearly concluded that use of the human study endpoint was appropriate for human health risk assessment, the current risk assessment continues to provide results using all three endpoints considered, but focuses on the results of the human study since these data best reflect human response to the chemical. Because these human data are considered reliable, and the study is considered scientifically valid, at this time the Agency considers the human study to be the most suitable for risk assessment purposes for this single-chemical risk assessment.

Dose Response Assessment

Acute RfD

In order to evaluate the appropriate point of departure (PoD) for ChEI, the Agency considered benchmark dose (BMD) estimates developed from the human acute oral study. In an acute oral study conducted in human volunteers of both sexes, aldicarb treatment resulted in statistically-significant inhibition of both red blood cell and plasma cholinesterase at the two common dose levels of 0.025 and 0.050 mg/kg. Although use of data from multiple studies provides a more robust analysis than a single study, for aldicarb there are data on the species of interest [human], there is a similarity in response between rats and humans at a common dose level [0.05 mg/kg], and there are data in the human at dose levels lower than those tested in the rat. At this time the Agency considers the human RBC ChE inhibition data to be sufficiently reliable for developing a point of departure (i.e., BMD and BMDL values were calculated) for risk assessment purposes for this single chemical risk assessment. Note that EPA's use of a human oral study in the aldicarb risk assessment is in accordance with the Agency's Final Rule promulgated on January 26, 2006, related to Protections for Subjects in Human Research, which is codified in 40 CFR Part 26.

Also considered were the benchmark dose (BMD) estimates developed from the rat acute and subchronic neurotoxicity studies and the non-guideline acute neurotoxicity study (Moser) along with BMD estimates provided in the preliminary cumulative risk assessment for N-methyl carbamates (NMC; presented to the FIFRA SAP in February and August, 2005; USEPA, 2005). In the previous analysis, the Agency used data from both the registrant's dose-response studies and from the Agency's comparative study (adult rat data only). The RBC ChE data from the aldicarb human study were utilized in the model in the same manner as the acute rat data (brain and RBC) that are available for the NMCs of the cumulative hazard assessment.

As previously stated, there was no evidence of increased sensitivity in developing animals in any of the guideline studies reviewed. Developmental toxicity was not seen in rats or rabbits nor were reproductive effects seen in the rat multi-generation reproduction study. Additionally, there was no developmental toxicity in the developmental neurotoxicity study in rats. However, the comparative ChE inhibition study [Moser] demonstrated that pups were more sensitive than the adults with respect to brain ChEI. Based on benchmark dose (BMD) estimates calculated from these data, the pups are 2X more sensitive than the adults [brain BMD_{10s} ranged from 0.014 to 0.020 in juvenile animals and 0.024 to 0.031 in adult animals]. Therefore, a FQPA safety factor of 2X is retained.

The acute reference dose (aRfD) for dietary exposure assessment was derived from the human RBC BMDL₁₀ as the point of departure [0.013 mg/kg] divided by an intraspecies factor of 10X and an interspecies factor of 1X, resulting in an acute RfD of 0.0013 mg/kg. Using the FQPA SF of 2X, the population adjusted dose (aPAD) is 0.00065 mg/kg. For additional risk characterization, aPADs using the rat brain and rat RBC BMDL₁₀ were determined. The aPAD based on rat brain ChEI is 0.00075 mg/kg and the aPAD based on rat RBC BMDL₁₀ is 0.0005 mg/kg/day. More detailed information about the derivation of these aPADs can be found in the *Dose Response* chapter in this document.

Chronic RfD

Aldicarb-induced inhibition of ChE activity is rapidly reversible (less than 24 hours). Therefore, chronic exposure to aldicarb is considered to be a series of acute exposures, and a separate chronic assessment is not necessary.

There are no residential uses of aldicarb; therefore, a residential exposure assessment was not conducted.

Dermal and Inhalation

There are no suitable dermal or inhalation toxicity studies for aldicarb risk assessment purposes. Therefore, the Agency selected the same dose and endpoint (0.013 mg/kg/day, based on RBC ChEI) for short-term dermal and inhalation risk assessments. The BMDL₁₀ value of 0.013 mg/kg/day in the human calculated from the RBC ChEI data is appropriate for assessing risks from dermal and inhalation exposure (all durations) for occupational workers (the most sensitive effect in the population of concern, adults). Only short- and intermediate term (i.e., no long term exposures) dermal and inhalation exposures are expected to occur based on the

use patterns for aldicarb. The target margin of exposure (MOE) is 10 (i.e., 10X for intraspecies variability and 1x for interspecies extrapolation).

The submitted dermal toxicity studies are considered unacceptable, and there is no dermal penetration study; therefore, dermal exposure assessments have been conducted assuming a default dermal absorption factor of 100% relative to oral dosing. A comparison of cholinesterase data from unacceptable dermal toxicity studies to cholinesterase data from oral studies suggests 100% dermal absorption is conservative, and therefore protective, for dermal exposures. An inhalation absorption factor of 100% relative to oral exposures was applied in assessing inhalation exposure and risk for aldicarb. In accordance with Agency policy, the FQPA SF does not apply to occupational assessments.

Exposure Assessment

The use pattern for aldicarb is expected to result in exposure to the general population through food and drinking water. There is a potential for inhalation exposure from aldicarb-treated tobacco, but there are no residential uses or agricultural uses that would result in residential exposure to the general population. Exposures can occur for occupational handlers loading or applying aldicarb granulars, but no postapplication exposure is expected because aldicarb is soil-incorporated at planting.

Aldicarb Exposure from Food

The residue chemistry database is essentially complete, including acceptable plant and animal metabolism studies, analytical methods, field residue trials, processing studies and rotational crop studies. The data are adequate for both tolerance reassessment and dietary exposure assessment. Aldicarb residues are not expected in livestock commodities such as meat, milk and eggs, and residues in most field crops are low or nondetectable. Higher residues (primarily of aldicarb metabolites and not aldicarb *per se*) have historically been found in monitoring of citrus and potato commodities, including individual oranges and potatoes.

HED conducted highly refined acute (probabilistic) dietary exposure assessments using the Dietary Exposure Evaluation Model (DEEM-FCID™) and consumption data from the US Department of Agriculture (USDA) Continuing Surveys of Food Intake by Individuals (CSFII, 1994-1996 and 1998.). The acute dietary exposure assessment incorporated monitoring and market basket survey data from the USDA Pesticide Data Program (PDP, potatoes and sweet potatoes) and the Carbamate Task Force (CTF, oranges). These three data sets were used to assess exposure from all potato and sweet potato food forms, as well as all citrus (orange, grapefruit, lemon and lime) food forms.

The PDP and CTF data were considered the best available data (for potatoes, sweet potatoes and citrus) for use in the dietary exposure assessments, since they reflect exposures closer to the point of consumption and would therefore be a more accurate representation of actual (i.e., "dinner plate") dietary exposure. For all other commodities, field trial data were used in the assessment, but residues were either very low or nondetectable (soybeans, cottonseed, peanuts, dry beans and coffee). Sugarbeet and sugarcane were excluded from the assessments, since

aldicarb residues are not expected in the processed commodities as consumed; the tolerance for sorghum was used in the assessment, but did not contribute significantly to estimated dietary exposure due to the low percent crop treated (%CT), the low tolerance, and low consumption.

Use information for aldicarb has been summarized in two Quantitative Usage Analyses (QUAs) generated by the Biological and Economic Analysis Division (BEAD), dated 12/99 and 5/00. The use information, including distinctions in %CT estimates for fresh vs. processed potatoes, oranges and grapefruit, was included in the dietary exposure analyses along with extensive processing/cooking data, generally indicating reduction of residues through boiling and juicing. Since aldicarb is systemic, typical food preparation practices such as washing and peeling are not expected to significantly reduce residues.

Estimated acute dietary (food only) exposure and risk do not exceed HED's level of concern [i.e., >100 % aPAD] for all population subgroups when compared to the human endpoint. The estimated dietary exposure and risk for the general U.S. population at the 99.9th percentile exposure using the human RBC ChEI endpoint was 0.000280 mg/kg/day, or 37% aPAD. For children 1 – 2 years old, the most highly exposed population subgroup, dietary exposure was 0.000592 mg/kg/day, or 78% aPAD. If the PAD is based on the rat RBC or brain ChEI endpoint, risk estimates for children 1-2 years old were 102% and 68%, respectively. For all population subgroups, residues in potatoes were the most significant source of dietary exposure. Sensitivity analyses showed that actual detected residues from monitoring are the source of the estimated exposure and risk, and not assumed residues for nondetects in the monitoring data sets. For example, in a sensitivity analysis which assumed aldicarb *per se* residues of 0 ppm in all potato and citrus commodities, and zero residues for citrus nondetects, the risk for the general US population was reduced from 37% to 36 %aPAD; for children 1-2 years old the estimated risk was reduced from 78% to 76 %aPAD at the 99.9th percentile of exposure when compared to the human RBC ChEI endpoint.

Aldicarb Exposure from Drinking Water

The OPP Environmental Fate and Effects Division (EFED) prepared the drinking water assessment for aldicarb reregistration. Aldicarb has the potential to reach surface and ground water sources of drinking water following applications in agricultural settings. The environmental fate database for aldicarb and its degradates (sulfoxide and sulfone) is incomplete but adequate for characterizing the potential for aldicarb residues to reach and to persist in ground and surface water sources of drinking water.

Total aldicarb residues (i.e., aldicarb plus the sulfoxide and sulfone degradates) are persistent and mobile in most soil types. The environmental profile is similar to that observed in plants, which consists of rapid oxidation of the parent aldicarb to aldicarb sulfoxide and sulfone, followed by breakdown to the relatively non-toxic non-carbamate residues. The degradates are more soluble in water than the parent.

EFED used Tier-II modeling to generate estimated environmental concentrations (EECs) for both surface water and groundwater sources of drinking water. Specifically, the Pesticide Root Zone Model and Exposure Analysis Model System (PRZM/EXAMS) Index Reservoir was used to generate surface water EECs and the PRZM model system was used to generate groundwater EECs for drinking water. For the purpose of the drinking water assessment, both surface and groundwater concentrations were reported for three vulnerable regions selected based on broad similarity in

aldicarb usage, crop type or soil conditions and which have the greatest potential for exposure to aldicarb. Additionally, for groundwater sources of drinking water, EECs were calculated based on proposed or established well setbacks ranging from 300 to 1000 ft. Total aldicarb residues are not expected to occur at levels that will contribute to dietary exposures for most of the country.

Aggregate Exposure

Since there is no potential for exposure to aldicarb and metabolites in residential settings, aggregate exposure and risk assessments include only dietary food and water sources of exposure.

The acute aggregate risk estimates when food and drinking water from surface water sources are assessed show HED's level of concern is not exceeded (<100% aPAD). The most highly exposed population subgroup was infants at 89% aPAD at the 99.9th percentile when compared to the human RBC endpoint.

Using the DEEM dietary model, the data indicate that aggregate exposure from food and ground water sources of drinking water is of concern for some regions including Florida which has a well setback of 1000 feet. Risk estimates ranged from 80 to 145% of the aPAD for children 1-2 years old and 53 to 285% of the aPAD for infants (<1 years old). These risk estimates are considered conservative since the food diaries used by Dietary Exposure Evaluation Model-Food Consumption Intake Database (DEEM-FCID Version 2.03) are based on total daily intake. The estimated risks are overestimates to the extent that food and drinking water are consumed throughout the day, rather than during only one event. Consequently, HED further refined the acute aggregate risk from food and groundwater by incorporating the time and amounts consumed for each eating occasion from the USDA CSFII food diaries to estimate exposures and risks on each eating occasion throughout the day and factoring in the cholinesterase-inhibition half-life related to aldicarb exposure. The eating occasion results are based on several major assumptions: (i) 2 hour half-life, (ii) allocation of direct drinking water consumption based on 6 equal and fixed occasions, and (iii) no modifications to the amount of indirect drinking water consumed as reported in the CSFII diaries for infants. Four drinking water (from groundwater sources) concentration scenarios were modeled for aldicarb: 3 ground water scenarios for aldicarb use on peanuts/cotton in Georgia with an assumption of 300 ft, 500 ft and 1000 ft well set backs, and one ground water scenario for aldicarb use on Florida citrus with a 1000 ft setback. The estimated risks at the per capita 99.9th percentile are below the level of concern for all four scenarios, and for all subpopulations except for infants under the Georgia 300 ft scenario(139% - 147% of the aPAD). For all other scenarios, risks are not exceeded for infants.

Aldicarb Exposure from Tobacco

Since aldicarb is registered for use on tobacco, HED conducted an inhalation risk assessment for adult smokers. The estimate of exposure was generated using high-end residues in smoke from aldicarb-treated tobacco, assumptions with respect to the frequency of smoking, and assuming that all of the aldicarb residue in smoke is absorbed (i.e., none of the residue is exhaled along with the smoke). Acute inhalation MOEs for aldicarb from the use of tobacco are estimated to be 104 for females and 121 for males; these MOEs are greater than the target MOE of 20, indicating that exposure and risk from aldicarb residues in tobacco are not of concern. These estimates are based on very conservative assumptions, and may overestimate exposure through this route.

Aldicarb Occupational Exposure and Risk

The occupational risk assessment for aldicarb is based on potential exposure to agricultural workers during loading and application of granular products. Aldicarb is applied early in the growing season, and labels require immediate soil incorporation of granules; postapplication exposures are not expected for workers, so a quantitative postapplication risk assessment has not been conducted. Two basic occupational handler scenarios, loading granules and applying granules, were assessed using exposures derived from a formulation- and chemical-specific study that monitored open loading and open-cab application conducted by the registrant (MRID 438525-01), the PHED (Pesticide Handlers Exposure Database), and a study which monitored granular closed loading and closed cab application in conjunction with high levels of personal protective equipment (i.e., MRID 447933-01 which was conducted using terbufos, data compensation issues may apply, this study was considered for comparative purposes based on comments from Bayer Crop Sciences).

The formulation- and chemical-specific study (MRID 438525-01) used aldicarb low-dust granules which are the only commercially marketed products. This study provides the most representative open loading and open cab application exposure estimates for aldicarb because of the low friability of aldicarb-containing products based on how it is formulated. PHED data are available for this scenario, and would be used in lieu of MRID 438525-01 if not available, but it is not recommended because exposure estimates would be based on the use of more friable clay granules which create more dust and, hence, higher exposure levels which would not be realistically expected. Aldicarb is also marketed in Lock-n-Load closed loading systems and it can be applied using closed cab tractors. As such, these exposures were also considered in this assessment. The aldicarb-specific study (MRID 438525-01) did not quantify the exposures associated with the use of these types of engineering controls. Instead, both PHED and the other study (MRID 447933-01) were used to evaluate exposures associated with closed loading systems and closed cab. The PHED-based values reflect the systems with normal work clothing and estimates from MRID 447933-01 reflect the use of aprons gloves for the loaders and coveralls with gloves for the applicators inside of a closed cab.

In this assessment, risks were calculated using an endpoint derived from a human administration toxicity study which was deemed appropriate based on the recent Agency Human Study Review Board meeting. The Agency believes that these estimates are the most relevant for considering risks for those occupationally exposed to aldicarb. In order to provide further characterization, the Agency also calculated risks based on rat endpoints (i.e., red blood cell and brain cholinesterase inhibition).

Aldicarb Incident Review

HED conducted a review of occupational and non-occupational incidents as reported in the Incident Data System (IDS) from 1996 through 1999 and in Poison Control Center (PCC) data generated from 1993 to 1998. Several incidents were reported from use in occupational settings. During this time, a total of 15 men were reported to be adversely exposed to aldicarb in occupational settings. Detailed information about these incidents is discussed in the Incident Data section of this document.

Aldicarb Data Gaps and Labeling

Toxicology:

- Comparative Cholinesterase Assay (PND 11 pups and adult rats)
- 1-day dermal toxicity study (including RBC/plasma/brain ChEI measures)
- 1-day inhalation toxicity study (including RBC/plasma/brain ChEI measures)

For aldicarb, the Agency has relied primarily on the non-guideline comparative cholinesterase study in juvenile and adult animals to evaluate the potential sensitivity of young animals to cholinesterase inhibition. However, RBC cholinesterase inhibition was not monitored in that study (whole blood, plasma, and brain). Additionally, there are no comparative cholinesterase activity recovery data available. Since RBC cholinesterase inhibition has been selected as endpoint for derivation for PODs in the aldicarb risk assessment, a comparative cholinesterase assay (PND 11 pups and adult rats) measuring cholinesterase activity (RBC and brain) is required. Time-course data for cholinesterase should be generated prior to the dose-response study, to determine time to peak effect and time to recover to control values (ChE activity). Protocols should be submitted to OPP for comment prior to study initiation.

Additionally, the previous data gaps of 21-day repeat dermal and repeat dose inhalation studies have been removed and replaced with the requirement for one-day dermal and one-day inhalation studies in which ChE activity (peak effect, time to recovery, dose response) is monitored. These studies will provide more useful data for risk assessment. Protocols should be submitted to OPP for comment prior to study initiation.

Residue Chemistry:

860.1500	Field trials in sorghum forage and cotton gin by-products (gin trash). [HED recommends cotton field trials include residues in cottonseed, since the available data for this commodity are limited and of poor quality.]
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Label Changes:

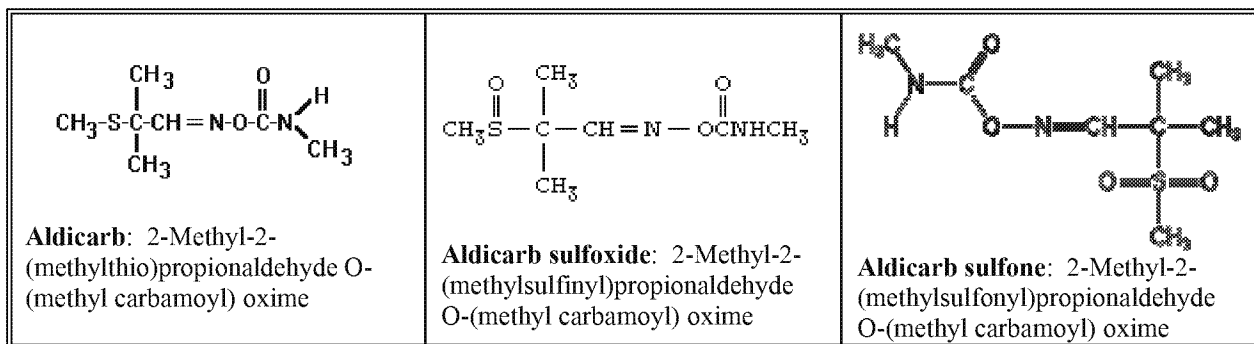
- Registered labels must reflect maximum seasonal use rates (where applicable).
- The restriction against feeding grain sorghum forage must be removed.
- A 10-month plantback interval (PBI) should be specified on EPA Reg. No. 264-331 for crops not listed on the label.

2.0 PHYSICAL/CHEMICAL PROPERTIES

Technical aldicarb is a white crystalline solid with a melting point of 98-100 C and a slight sulfurous odor. Crystalline aldicarb is heat-sensitive and decomposes above 100 C. Aldicarb is soluble in water (0.6%) and increasingly more soluble in the following solvents: hexane (<1%), carbon tetrachloride (4%), benzene (18%), methylethyl ketone (20%), acetone (38%), and chloroform (42%). The vapor pressure of technical aldicarb is 2.9×10^{-5} mm Hg at 25 C. Identifying codes and characteristics are:

Empirical Formula: $C_7H_{14}N_2O_2S$
Molecular Weight: 190.3
CAS Registry No.: 116-06-3
Chemical ID No.: 098301
Octanol/water partition coefficient (log Kow): 1.359
Density (at 25 C): 1.195

Structures of aldicarb and its two regulated metabolites, aldicarb sulfoxide and aldicarb sulfone, are shown below:



3.0 HAZARD ASSESSMENT

3.1 Hazard Profile

Aldicarb is a N-methyl carbamate pesticide that exerts its pesticidal activity and elicits adverse toxic effects by inhibition of cholinesterase activity [ChEI], which has been demonstrated in whole blood, plasma, red blood cells, and brain of rats, mice, and dogs following acute, subchronic, and chronic exposure and in plasma and RBC in humans following acute exposure.

The available data indicate a peak effect within an hour of dosing followed by recovery within 24 hours. As a result, a comparable degree of inhibition occurs whether delivered once or following subchronic or chronic dosing.

There is an acute oral exposure study on aldicarb involving direct dosing of humans in which plasma and RBC cholinesterase activity and clinical signs were monitored. There is also a full database of oral animal toxicity studies.

Aldicarb is highly acutely toxic via the oral, dermal, and inhalation routes of exposure in the acute studies required for labeling (Toxicity Category I). It is not considered to be a dermal sensitizer; dermal and eye irritation studies were waived due to severe effects (death) following corneal and dermal dosing.

Subchronic toxicity studies demonstrate that aldicarb inhibits cholinesterase activity in plasma, red blood cells (RBC), and brain in dogs, rats, and rabbits following exposure by the oral and dermal routes. Clinical signs associated with cholinesterase inhibition (ChEI) observed in subchronic studies include tremors, salivation, lacrimation, lethargy, and prostration.

The database for chronic toxicity is complete. There were no treatment-related effects on hematology, clinical chemistry [other than ChE activity], organ weights, and histopathology. Only scattered effects on other measures at the high dose were noted, such as decreased body weight and eye effects in rats.

The aldicarb database for neurotoxicity is complete, with acceptable acute, subchronic, and developmental neurotoxicity studies. In addition, there is a published acute neurotoxicity study from an EPA laboratory on the comparative sensitivity of young and adult rats following acute oral exposures. Both the acute and subchronic rat neurotoxicity studies show a variety of typical clinical signs of ChEI after oral exposures, including decreased motor activity, lacrimation, tremors, salivation, pinpoint pupils, and decreased grip strength, as well as significant decreases in plasma, RBC, and brain cholinesterase activity. In the developmental neurotoxicity study in rats, ChEI and associated clinical signs, i.e., tremors, salivation, lacrimation, ataxia, miosis, and hunched posture, were observed in the dams at the same dose levels where decreased motor activity was observed in the pups. No neuropathological effects related to exposure were seen in any of the acute, subchronic, chronic, or neurotoxicity studies.

There was no indication of increased susceptibility of offspring in rat or rabbit developmental toxicity studies, in the rat reproduction study, or in a rat developmental neurotoxicity study. In the developmental toxicity study in rabbits, no developmental effects were observed at any dose level, but maternal toxicity was observed, as evidenced by decreased body weight, pale kidneys, and hydroceles on the oviducts. In the developmental toxicity study in rats, the developmental effects, ecchymosis (hemorrhagic spots) of the trunk, occurred at the same dose level as the maternal effects, decreased body-weight gain and food consumption. Signs of ChEI including hypoactivity, ataxia, tremors, lacrimation and cold extremities were observed in the maternal rats. In the reproduction study, the effects on the offspring, reduced survival (day 4) and decreased body weight, were observed only at the highest dose tested where parental toxicity occurred, as evidenced by decreased body weight and blood cholinesterase inhibition. Maternal toxicity was observed at a dose where no offspring toxicity was observed (i.e., the NOAEL for maternal toxicity was lower than the offspring NOAEL).

A published acute oral exposure study (EPA/ORD; Moser) reported evidence for increased sensitivity of young rats. The only parameter that demonstrated sensitivity was brain cholinesterase inhibition (i.e., the magnitude of the brain ChEI was greater in the young rat compared to the adult rat at comparable acute doses). Decreased motor activity was observed

only in the adult animals, and clinical signs of ChEI occurred more frequently in, and recovery was prolonged in, the adult compared to the young animal. Sensitivity with respect to the whole blood compartment could not be determined since whole blood ChEI was extremely high in this compartment at all dose levels in both the young and adult animal.

In an acute oral study conducted in human volunteers of both sexes, red blood cell and plasma cholinesterase activities and clinical signs were monitored. Aldicarb treatment of both males and females resulted in statistically significant inhibition of both red blood cell and plasma cholinesterases at the two common dose levels. The inhibition observed at the lowest dose, which was tested only in males, was not considered toxicologically significant in males; *i.e.* *RBC ChEI* <10%; *plasma ChEI* <20%. However, there is a lack of dose-response information in females at the low dose level. Ratios of the BMDL_{10s} for RBC ChE inhibition suggest a two-fold difference in toxic responses between animals and humans. This study was evaluated by the HSRB, and they arrived at similar conclusions.

Aldicarb is rapidly absorbed, widely distributed, and rapidly excreted, with more than 90% excreted in the urine within 24 hours after either acute or repeated oral doses. It is metabolized primarily to aldicarb sulfoxide, with a smaller amount then slowly converted to aldicarb sulfone. These three moieties (aldicarb, sulfoxide, and sulfone) may then be further metabolized to oximes and nitriles. Both the sulfoxide and sulfone are also potent cholinesterase inhibitors. The sulfone is less toxic following an acute oral exposure than either the parent compound or the sulfoxide which show comparable acute oral toxicity, based on results of median lethal dose studies (*i.e.*, LD50's).

There are acceptable negative studies for all three required categories of mutagenic effects: gene mutations, chromosomal aberrations, and other genotoxic effects. Aldicarb was negative in the *in vitro* forward gene mutation assay, in the *in vivo* chromosomal aberration assay in mouse bone marrow cells, in the dominant lethal assay, and in the unscheduled DNA synthesis assay. Based on these studies, aldicarb is not considered mutagenic.

Aldicarb is classified as Category E, Evidence of Non-Carcinogenicity for Humans, based on the lack of evidence of carcinogenicity in studies in rats and mice and the absence of a mutagenicity concern.

There are no acceptable dermal toxicity or dermal penetration studies that can be used, when considered with all available oral studies, to estimate dermal absorption for occupational exposure and risk assessments. In this risk assessment, toxicity by the dermal route has been considered to be equivalent to toxicity by the oral route of exposure (100 %). Additionally, there is no inhalation toxicity study, and toxicity by the inhalation route also has been considered to be equivalent to toxicity by the oral route of exposure (100 %). Table 1 summarizes the results of acute toxicity testing for aldicarb.

Table 1. Aldicarb Acute Toxicity.

Guideline No./Study Type	MRID No.	Results	Tox Category
870.1100 Acute oral toxicity	00057333	LD ₅₀ = 0.8 mg/kg/day	I
870.1200 Acute dermal toxicity	00091241 00069916	LD ₅₀ = 20 mg/kg/day, water LD ₅₀ = 5 mg/kg, propylene glycol	I
870.1300 Acute inhalation toxicity	00069916 00057333	LC ₅₀ < 0.007 mg/L	I
870.2400 Acute eye irritation	00069916	No corneal irritation at lethal dose	N/A
870.2500 Acute dermal irritation	00069916	None at fatal levels	N/A
870.2600 Skin sensitization	N/A	N/A	N/A

The above studies satisfy the acute toxicity data requirements [OPPTS 870.1100, 870.1200, 870.1300]; dermal and eye irritation studies not required due to severe effects [death] following eye and dermal exposure; (N/A = not applicable). Table 2 summarizes the toxicity profile for technical aldicarb.

Table 2. Toxicity Profile of Aldicarb Technical.

Study Type [GLN No.]	MRID No./Classification	Results ¹
Sub-chronic oral toxicity (dog) [870.3150]	41919901 (1991) Acceptable	NOAEL=0.02 mg/kg/day LOAEL=0.06 mg/kg/day Based on plasma and RBC ChEI in males and females
Developmental toxicity rodent (rat) [870.3700a]	41004501 (1988) Guideline	Maternal: NOAEL=0.125 mg/kg/day LOAEL=0.25 mg/kg/day Based on decreased body weight gain and food consumption Developmental: NOAEL=0.125 mg/kg/day LOAEL=0.25 mg/kg/day Based on ecchymosis of the trunk
Developmental toxicity in non-rodent (rabbit) [870.3700b]	0132668 (1983) Guideline	Maternal: NOAEL=0.1 mg/kg/day LOAEL=0.25 mg/kg/day Based on decreased body weight, pale kidneys, hydroceles on the oviducts Developmental: NOAEL=>0.5 mg/kg/day
Reproduction and fertility effects [870.3800]	42148401 (1991) Minimum	Parental/Systemic NOAEL=0.4 mg/kg/day LOAEL=0.7-0.9 mg/kg/day Based on decreased body weight gains and RBC and plasma ChEI Reproductive: NOAEL=0.7-0.9 mg/kg/day LOAEL=1.4-1.7 mg/kg/day Based on decreased viability and body weights, and signs of debilitation

Table 2. Toxicity Profile of Aldicarb Technical.

Study Type [GLN No.]	MRID No./Classification	Results¹
Chronic oral toxicity in rodents [870.4100a]	43045401 (1993) Minimum	NOAEL=0.047 mg/kg/day LOAEL=0.47 mg/kg/day Based on plasma and RBC ChEI
Chronic oral toxicity dogs [870.4100b]	40695401, 42191501 (1988) Supplementary	NOAEL<0.028 mg/kg/day LOAEL=0.028 mg/kg/day Based on plasma ChEI
Carcinogenicity in rats [870.4200]	43045401 (1993) Minimum	NOAEL=0.047 mg/kg/day LOAEL=0.47 mg/kg/day Based on plasma/RBC ChEI No evidence of carcinogenicity
Carcinogenicity in mice [870.4300]	00044732; 00044733; 00044734 (1972) Minimum	NOAEL=0.2 mg/kg/day LOAEL=0.4 mg/kg/day Based on increased mortality. No evidence of carcinogenicity.
Gene Mutation [870.5300]	00148168 (1985) Acceptable	1000-5000 ug/ml: Negative with and without activation at a marginally cytotoxic dose.
Cytogenetics: Mammalian bone marrow chromosome aberration test. [870.5385]	41661301; 41663102 (1990) Acceptable	0.1-0.4 mg/kg: No chromosomal aberrations in mouse bone marrow cells.
Unscheduled DNA Synthesis [870.5500]	00141673 (1984) Acceptable	33-10,000 ug/well: No effects.
Rat Dominant Lethal Study	43575101 (1995) Acceptable	Systemic LOAEL: 2.28 mg/kg Based on body weight reductions, tremors, and plasma, RBC and brain ChEI. No evidence of a dominant lethal effect.
Acute neurotoxicity screening battery [870.6200a]	43442301 (1994) Acceptable	NOAEL<0.05 mg/kg/day LOAEL=0.05 mg/kg/day Based on plasma ChEI.
Subchronic neurotoxicity screening battery [870.6200b]	43829602 (1995) Acceptable	NOAEL<0.05 mg/kg/day LOAEL=0.05 mg/kg/day Based on pinpoint pupils and blood and brain ChEI.
Developmental neurotoxicity [870.6300]	43829601 (1995) Acceptable	Maternal: NOAEL=0.05 mg/kg/day LOAEL=0.1 mg/kg/day Based on plasma ChEI Offspring: NOAEL=0.05 mg/kg/day LOAEL=0.1 mg/kg/day Based on reduced body weights and decreased motor activity
Metabolism and pharmacokinetics [870.7485]	00102022 (1966) 00102023 (1967)	85% of an acute oral dose to rats was excreted in 24 hours. The metabolism of aldicarb was primarily to the sulfoxide (40%), with a smaller amount then slowly converted to the sulfone.
Special neurotoxicity studies: Moser VC	45068601 (1999) TAP 157 94-106	NOAEL<0.05 mg/kg. LOAEL=0.05 mg/kg (pups) Effects in pups: Blood (both sexes), brain ChEI (males). Note: PND 17 day pups exhibited twice the level of brain ChEI as adults.

Table 2. Toxicity Profile of Aldicarb Technical.

Study Type [GLN No.]	MRID No./Classification	Results ¹
Acute oral study (human) Inveresk	42373001 (1992) 46131001 (supplementary report)	NOAEL = not determined for females LOAEL = 0.01 mg/kg

¹NOAEL = No observed adverse effects level; LOAEL = Lowest observed adverse effects level; ChE = Cholinesterase; ChEI = Cholinesterase inhibition; RBC = red blood cell.

3.2 Dose Response Assessment

3.2.1 Benchmark Dose (BMD) Analysis

In order to evaluate the appropriate point of departure (PoD) for ChEI, the Agency considered benchmark dose (BMD) estimates developed from several studies as mentioned above along with BMD estimates provided in the preliminary cumulative risk assessment for the N-methyl carbamates (USEPA, 2005). Dose-response modeling is preferred over the use of NOAEL/LOAELs (i.e., no or lowest observed adverse effect levels) since NOAELs and LOAELs do not necessarily reflect the relationship between dose and response for a given chemical, but instead reflect dose selection (USEPA, 2000). The estimated dose at which 10% ChEI is observed (BMD₁₀) and the lower 95% confidence intervals (BMDL₁₀) were estimated by fitting the ChE data to an exponential dose-response model using generalized nonlinear least squares. The BMD₁₀ was selected because it is generally at or near the limit of sensitivity for discerning a statistically significant decrease in ChE activity across the blood and brain compartments and is a response level close to the background ChE activity. Moreover, the Agency believes that 10% is likely to be protective for other toxicities, such as clinical signs and/or behavioral endpoints.

The Agency's BMD analysis for the preliminary cumulative risk assessment was presented to the FIFRA SAP in February and August, 2005. At those meetings, the panel supported the Agency's approach for developing BMD estimates for the N-methyl carbamates. In the current analysis, the Agency used ChE inhibition data for RBC from the human study. Ratios of the BMD_{10s} for brain ChE inhibition between juvenile and adult animals suggest that juvenile animals are 2X more sensitive than adult animals. Therefore, the Agency has retained a 2X FQPA safety factor in the derivation of the aldicarb acute PAD and other acute risk assessments.

The human toxicity study for aldicarb provides RBC and plasma ChE data for both males and females. The blood ChE activity data (plasma and RBC) provided in the human study are considered appropriate surrogate measures of potential effects on peripheral nervous system (PNS) acetylcholinesterase (AChE) activity, and of potential effects on the central nervous system (CNS) when brain ChE data are lacking which is in accordance with the 2000 Science Policy on Use of Cholinesterase Inhibition in Risk Assessment of OPs and Carbamates (USEPA, 2000). AChE is the target enzyme for the cumulative risk assessment and is the primary form of ChE found in RBCs. The RBC data from the human study are being utilized by the Agency in this single chemical risk assessment.

The measured RBC ChE activity from the human study is adequate for estimation of BMD and BMDLs. The RBC ChE data from the aldicarb human study was utilized in the model in the same manner as rat data (brain and RBC) that are available for the NMCs of the cumulative hazard assessment (USEPA 2005). The BMD₁₀ and BMDL₁₀ estimates for both rat (RBC, brain) and human (RBC) are included in Table 3 below.

Table 3. Oral BMD_{10s} and BMDL_{10s} Generated from Adult Rat ChE (RBC, brain) and Human ChE (RBC) Data for Aldicarb.						
Chemical	Rat				Human	
	Brain		RBC		RBC	
	BMD ₁₀ (mg/kg)	BMDL ₁₀ (mg/kg)	BMD ₁₀ (mg/kg)	BMDL ₁₀ (mg/kg)	BMD ₁₀ (mg/kg)	BMDL ₁₀ (mg/kg)
Aldicarb	F=0.05 M=0.06	F=0.03 M=0.03	0.03	0.02	0.02	0.01
BMD estimates are presented as a single estimate when there are no differences between sexes. Human RBC data obtained from MRID 42373001 Rat brain and RBC data obtained from MRIDs 43442302, 43442305, 43829601, 43829602, 45068601.						

3.2.2 Endpoint Selection

Based on the toxicity profile, the Agency has selected endpoints and doses for assessment of risk. The Agency considered the human acute oral study for assessment of the acute exposure scenarios. Due to recovery of ChEI within 24 hours following aldicarb exposure, the use of the acute study in humans for endpoint selection is considered appropriate and protective for all exposure durations (repeated dosing is considered a series of acute exposures).

For aldicarb, the similarity of response between humans and rats following acute oral exposure allows for the use of both sets of data in considering toxicity endpoint selection and uncertainty factors. As mentioned previously in an acute oral study conducted in human volunteers, aldicarb treatment of both males and females resulted in statistically-significant inhibition of both red blood cell and plasma cholinesterases at the two common dose levels. Although brain ChEI is not available from the human study, the RBC activity is considered appropriate surrogate measures of potential effects on peripheral nervous system (PNS) acetylcholinesterase (AChE) activity, and of potential effects on the central nervous system (CNS) when brain ChE data are lacking (USEPA 2000). In addition, the human RBC ChEI observed in both sexes at the two common dose levels suggest no differences between sexes in humans. Note that EPA's use of a human toxicity study in the aldicarb risk assessment is in accordance with the Agency's Final Rule promulgated on January 26, 2006, related to Protections for Subjects in Human Research, which is codified in 40 CFR Part 26. The final report of the HSRB as it relates to aldicarb is available at <http://www.epa.gov/osa/hsrb/files/april2006mtgfinalreport62606.pdf>

There are several rat studies available where acute ChE inhibition was measured at or near peak time of inhibition (45 minutes –1hour) and these inform the derivation of the acute RfD and acute PAD. These include the acute and subchronic neurotoxicity studies performed by the registrant and an acute comparative ChE activity study performed by scientists from the National Health and Environmental Effects Research Laboratory (NHEERL). Clinical signs were also reported in these studies, but usually only at the higher dose levels; i.e., ChEI occurred

at doses lower than or equal to dose levels where clinical signs occurred. It is unknown whether changes in clinical signs indicative of ChEI are related to brain or peripheral ChE inhibition; the Agency cannot discount the potential that peripheral ChE inhibition may be produced by aldicarb. Given that numerous studies have shown RBC ChE inhibition to be a sensitive measure and that dose-related changes in behavioral endpoints and clinical signs have been observed at the higher doses of aldicarb, at this time, the Agency considers the RBC ChE inhibition data to be sufficiently reliable for developing a point of departure for risk assessment purposes.

To repeat there are no suitable dermal or inhalation toxicity or dermal penetration studies for aldicarb risk assessment. Therefore the same study is considered appropriate for endpoint selection for short and intermediate term occupational dermal and inhalation exposure.

Additionally, based on the recovery of effects within 24 hours seen in both the human and animal studies and on the fact that repeat dosing is considered a series of acute exposures, the same toxicity study was considered for establishing a chronic RfD and for assessing long-term occupational risk. However, the Agency has determined that a chronic risk assessment is not needed, since risks resulting from aldicarb exposure are better described as a series of acute risks, and since chronic risk estimates will necessarily be lower than acute risk estimates since average rather than high-end exposure estimates are used with the same POD.

Table 4 presents the toxicity endpoints for risk assessment.

The registrant submitted rat 21-day and 5-day dermal toxicity studies in which the granular formulation containing 14.75 % ai was used as the test substance, rather than the technical active ingredient. These studies had inconsistent findings with respect to body weight gains and ChEI data, and were considered unacceptable for the purpose of risk assessment. HED had concerns about the extent of wetting of the skin, as well as the percentage of body surface area treated, which may have contributed to the lack of a dose-response. The Hazard Identification Assessment Review Committee (HIARC) discussed the data from these two studies, along with ChEI data from oral studies of varying durations, in order to determine if a weight-of-evidence-based dermal absorption factor could be derived. Although the HIARC agreed that most of the data suggest a dermal absorption factor of less than 100%, inconsistencies in the data and methodology concerns prevented a possible departure from the use of 100% absorption for dermal exposure assessments. This value is thought to be conservative, and, therefore, protective for dermal exposures.

Likewise, for inhalation exposures assessed using oral studies, the HIARC selected an inhalation absorption factor of 100% relative to oral exposures to be applied in assessing inhalation exposure and risk for aldicarb.

Table 4. Aldicarb Toxicology Endpoint Selection.

Exposure Scenario	Dose Used in Risk Assessment, UF ¹	FQPA SF and Reference Dose for Risk Assessment	Study and Toxicological Effects
DIETARY EXPOSURES			
Acute Dietary: General US Population [MRID No. 42373001]	BMDL10 = 0.013 mg/kg UF = 10 Acute RfD = 0.0013 mg/kg/day	FQPA SF = 2X $aPAD = \frac{\text{acute RfD}}{\text{FQPA SF}}$ = 0.00065 mg/kg/day	human study RBC ChEI
Chronic Dietary: General US Population [MRID No 42373001]	BMDL10 = 0.013 mg/kg UF = 10 Chronic RfD = 0.0013 mg/kg/day	FQPA SF = 2X $cPAD = \frac{\text{chronic RfD}}{\text{FQPA SF}}$ = 0.00065 mg/kg/day	human study ChEI
DERMAL EXPOSURES			
Short-Term (1-30 days); Intermediate-Term (30 days to several months) [MRID No. 42373001]	Oral study BMDL10 = 0.013 mg/kg Absorption factor = 100%	LOC for MOE = 10	human study RBC ChEI human study [reduction of interspecies factor to 2X]
INHALATION EXPOSURES			
Any Duration [MRID No 42373001]	Oral study BMDL10 = 0.013 mg/kg Absorption factor = 100%	LOC for MOE = 10	human study RBC ChEI human study [reduction of interspecies factor to 2X]

1 The UF 10X is for intraspecies variability

2 Appropriate route-to-route extrapolation should be performed for these risk assessments. For both dermal and inhalation risks, a 100% absorption factor should be used to convert relevant exposure estimates to equivalent oral doses and compared to the oral LOAEL.

For informational purposes, Table 5 shows aPADs using the rat brain and rat RBC BMDL₁₀ for comparison with the aPAD based on the human RBC BMDL₁₀.

Table 5. Comparison of Population Adjusted Dose			
Parameter	Rat ³		Human ⁴
	Brain	RBC	RBC
BMD ₁₀ (mg/kg) ¹	F=0.05 M=0.06	0.03	0.02
BMDL ₁₀ (mg/kg) ²	0.03	0.02	0.013
UF (intraspecies)	10X	10X	10X
UF (interspecies)	2X	2X	1X
FQPA SF	2X	2X	2X
Acute RfD	0.0015	0.001 mg/kg	0.0013
Acute PAD	0.00075	0.0005 mg/kg	0.00065
1. BMD estimates are presented as a single estimate when there are no differences between sexes. 2. BMDL ₁₀ used for risk assessment 3. Rat brain and RBC data obtained from MRIDs 43442302, 43442305, 43829601, 43829602, 45068601. 4. Human RBC data obtained from MRID 42373001			

3.3 Reversibility

Aldicarb toxicity is characterized by maximal inhibition of cholinesterase which occurs rapidly followed by recovery typically occurring within hours. A key consideration in risk assessment is appropriate matching of the duration of exposure with the duration of the toxic effect.

Typically, HED's food and water exposure assessments sum exposures over a 24 hour period. This 24 hour total is typically used in acute dietary risk assessment. In the case of the aldicarb, because of the rapid nature of aldicarb toxicity and recovery, it may be appropriate to consider durations of exposure less than 24 hours. Conceptually, a physiologically-based pharmacokinetic model and/or biologically-based dose-response model would be available to account for the dynamic nature of exposure, absorption, toxicity, recovery, and elimination of aldicarb in animals and humans. However, such a model does not exist at this time. In the interim, HED has developed an analysis using information about external exposure, timing of exposure within a day, and half-life of ChE inhibition from rats and humans to estimate risk to aldicarb at durations less than 24 hours. Specifically, HED has evaluated individual eating and drinking occasions and used the ChE half-life information to estimate the residual effects from aldicarb from previous exposures within the day.

Table 6 below provides information on the recovery of ChE inhibition in rats and human subjects. For both species, the recovery half-life for RBC ChE inhibition is approximately two hours. At high doses in rat, the half-life is up to approximately 6 hours in females. The estimates of half-life at the lower doses are most relevant for risk assessment and are thus the

focus here. As can be seen in the table, the estimated recovery half life of aldicarb-inhibited AChE in the human is estimated to be on the order of 2 hours using RBC AChE activity. This 2 hour recovery half-life is what is used in this refined dietary exposure assessment which incorporates information on eating/drinking occasions. There is some uncertainty associated with the use of the two hour recovery half-life. As discussed in detail below, infants and children are the focus of the current analysis. Although there are dose-response ChE data in juvenile animals exposed to aldicarb, there are no such data to characterize ChE recovery in the young. As such, the Agency has assumed that the half-life to recovery in the young is similar to that seen in adults. The Agency is requiring such data in young animals to confirm this assumption.

Table 6. Recovery half-life information for ChE inhibition following oral exposure to aldicarb in rats and human subjects

Chemical	Brain		RBC	
	Recovery Half-Life Estimate (hrs)	Upper & Lower Confident Intervals (hrs)	Recovery Half-Life Estimate in hrs (dose; mg/kg)	Upper & Lower Confident Intervals (hrs)
Rat	1.52	1.16-1.99	F (< 0.1) 1.10 (0.1,0.3) 2.91 (0.3,0.5) 3.39 (>0.5) 5.90 M (<0.1) 1.91 (0.1,0.3) 1.20 (0.3,0.5) 1.62 (>0.5) 1.50	F 0.50-2.40 1.96-4.33 2.35-4.90 3.52-9.91 M 1.31-2.79 0.87-1.64 1.19-2.21 0.80-2.82
Human	N/A		2.07	1.74-2.46

3.4 FQPA Considerations

The FQPA (1996) instructs EPA, in making its “reasonable certainty of no harm” finding, that in “the case of threshold effects, an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and postnatal toxicity and completeness of data with respect to exposure and toxicity to infants and children.” Section 408 (b)(2)(C) further states that “the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children.”

There was no evidence of increased sensitivity in any of the guideline studies reviewed. Aldicarb did not result in developmental toxicity in either rats or rabbits or in reproductive effects in the rat multi-generation reproduction study. Additionally, there was no developmental toxicity in the developmental neurotoxicity study in rats. However, the comparative cholinesterase inhibition study [Moser], in which adult and

juvenile rats were exposed to the same acute oral doses of aldicarb, demonstrated that juvenile rats were more sensitive than the adults with respect to brain cholinesterase inhibition. Based on benchmark dose (BMD/BMDL) estimates calculated from these data, the young animals are 2X more sensitive than the adults [brain BMD10s ranged from 0.014 to 0.020 in juvenile animals and 0.024 to 0.031 in adult animals]. Therefore, a FQPA safety factor of 2X is retained.

3.5 Endocrine Disruption

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) “may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate.” Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC’s recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

In the available toxicity studies on aldicarb, there was no estrogen, androgen, and/or thyroid mediated toxicity.

When additional appropriate screening and/or testing protocols being considered under the Agency’s EDSP have been developed, aldicarb may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

4.0 EXPOSURE ASSESSMENT AND CHARACTERIZATION

4.1 Summary of Registered Uses

Aldicarb is a carbamate pesticide which is registered for use as a systemic insecticide, acaricide and nematicide on agricultural crops including citrus, cotton, dry beans, peanuts, pecans, potatoes, sorghum, soybeans, sugar beets, sugarcane, sweet potatoes, and seed alfalfa (CA). In addition, aldicarb may be applied to field grown ornamentals (CA) and tobacco, and on coffee grown in Puerto Rico. The types of plant pests controlled by aldicarb include leaf phylloxera; bud moth; citrus nematode; aphids; mites (citrus red, citrus rust, Texas citrus); white flies; thrips; fleahoppers, leafminers; leafhoppers; overwintering boll weevil (adults feeding on foliage); lygus; nematodes; cotton leaf perforator; seedcorn maggot; Mexican bean beetle; flea beetles; Colorado potato beetle; greenbug; chinch bug; three cornered alfalfa hopper (suppression); and

sugar beet root maggot.

Aldicarb is a restricted use pesticide (RUP), and may be applied only in occupational settings by certified applicators. There are no products containing the active ingredient aldicarb which are intended for sale to homeowners or in non-occupational settings (e.g., turf or golf course).

Aldicarb is formulated and marketed solely as a granular pesticide. Aldicarb in a vinyl binder coating is adhered to either a corn cob grit or gypsum substrate; these two substrates produce less dust than typical clay substrates used for granular pesticides. Only the gypsum granular is available in closed loading systems. The formulations consist of 5, 10 and 15% granulars, which are applied early in the growing season, either pre-plant, at-planting, or early post-emergent, using ground application equipment. Labels specify use of positive displacement application equipment and immediate soil incorporation.

For most crops, only one aldicarb application per season is allowed, but 2 or 3 split applications are permitted on sugar beets. The pre-harvest intervals (PHIs) are generally long due to the early application timing, ranging from 80 to 150 days when specified.

Use information for aldicarb has been summarized in two Quantitative Usage Analyses (QUAs) generated by BEAD/OPP, dated 12/99 and 5/00. Estimates of the amount of active ingredient applied on a crop-specific basis have been provided based on data from EPA, USDA, the National Center for Food and Agricultural Policy, and the WEFA group. In terms of pounds of active ingredient (ai) applied, the most significant use site for aldicarb is cotton, with 2 to 3 million lbs ai applied on an annual basis. Other significant use sites (in decreasing amounts of ai applied) are peanuts, potatoes, sugar beets and oranges. Based on acres grown and pounds active ingredient applied, BEAD generates estimates of the percent of crop treated (%CT) for use in HED's dietary exposure analyses. For aldicarb, crops with %CT estimates of greater than 20% are peanuts, sweet potatoes, cotton, potatoes and citrus.

4.2 Dietary Exposure/Risk Pathway

Potential dietary (food only) exposure to aldicarb can occur following application to food crops including pecans; potatoes; sweet potatoes; cotton; dry beans; grain sorghum; soybeans; sugar beets; sugarcane; peanuts; citrus (orange, grapefruit, lemon and lime); and coffee.

4.2.1 Residue Profile

The aldicarb residue chemistry database is largely complete and is considered adequate to reassess most tolerances listed in 40 CFR §180.269. The regulated residues are the combined residues of aldicarb and its two cholinesterase-inhibiting metabolites aldicarb sulfoxide [2-methyl-2-(methylsulfinyl)propionaldehyde O-(methyl carbamoyl) oxime] and aldicarb sulfone [2-methyl-2-(methylsulfonyl)propionaldehyde O-(methyl

carbamoyl) oxime]. Aldicarb sulfoxide is considered to have similar potency to the parent in terms of toxicity, while aldicarb sulfone is less potent. Aldicarb and the sulfoxide and sulfone metabolites are the residues of concern for both tolerance reassessment and risk assessment purposes. Currently established tolerances for aldicarb and its metabolites range from 0.002 ppm in milk to 1 ppm in potatoes.

The metabolic breakdown and nature of aldicarb residues in plants and livestock are adequately understood, based on metabolism studies conducted in lemons, cotton, peanuts, potatoes, and sugar beets, and in ruminants and poultry. These studies have shown that following soil application, aldicarb is readily taken up through root systems and translocated throughout the plant. Aldicarb is oxidized to form the cholinesterase-inhibiting metabolites aldicarb sulfoxide and aldicarb sulfone. Further hydrolysis of the cholinesterase-inhibiting parent and metabolites yields the (less toxic) oxime, acid, nitrile and alcohol derivatives of the carbamate metabolites. The metabolic pathway in livestock is similar to that observed in plants; in addition, the tentative identification of radiolabeled fatty acids and glycerol in eggs, and the significant levels of dispersed radioactivity in the chromatograms of tissue extracts, suggest incorporation of degraded aldicarb into the biochemical pathway.

Adequate data collection and enforcement analytical methods are available for aldicarb and its metabolites. The enforcement method involves oxidation of aldicarb and aldicarb sulfoxide to aldicarb sulfone; total residues are quantified as the sulfone (Pesticide Analytical Manual, Volume II, Method II) using gas-liquid chromatography with flame photometric detection in the sulfur mode (GLC/FPD). Data collection methods that have been used to generate residue data in certain commodities (e.g., potatoes and citrus) separately quantify aldicarb and its metabolites using high performance liquid chromatography (HPLC).

Aldicarb and aldicarb sulfone residues are completely recovered (>80%) using multiresidue method PAM Volume I Section 302 (Luke method; Protocol D) and Section 401 (method for N-methylcarbamates). Aldicarb sulfoxide residues are also completely recovered using multiresidue method Section 302, but are only partially recovered (50-80%) using Section 401.

In most raw agricultural commodities (RACs), aldicarb and metabolite residues are expected to be low or nondetectable; however, in the past, higher residues have been known to occur in individual citrus (orange and grapefruit), potatoes and sweet potatoes. In general, the parent, aldicarb *per se* is not detected in plants; residues of aldicarb sulfoxide tend to be detected more often and at higher levels than aldicarb sulfone.

Residues of concern are not likely to be detected in livestock tissues, milk and eggs, and HED has previously recommended against establishing tolerances for residues in poultry commodities. HED has recommended revocation of existing tolerances for aldicarb residues in livestock commodities. Aldicarb and metabolite residues generally do not concentrate during processing, with the exception of certain dried commodities. Since aldicarb is a systemic pesticide, food preparation activities such as washing and peeling are not likely to reduce residues; however, special studies in potatoes have shown a

reduction in residues during baking (oven) and boiling. There is a potential for uptake of residues in rotational crops; therefore, rotational crop tolerances or adequate plantback intervals have been recommended.

Extensive monitoring data for aldicarb have been generated in composite samples of numerous commodities and in multiple years by the USDA Pesticide Data Program (PDP) and the FDA Surveillance Monitoring Program. Monitoring data reflect residues in commodities closer to the point of consumption (i.e., "dinner plate") rather than the maximum residues generated in field trials, and can be used in dietary exposure analyses to determine a more realistic estimate of dietary exposure and risk. In addition to the composite commodity samples routinely analyzed by USDA, PDP conducted a special study on aldicarb in potatoes during 1997, which was designed to provide a comparison between a composite residue value and the distribution of residues within that sample on a single-serving basis. The study included measurements of aldicarb residues in composite samples and individual potatoes within those composites. Aldicarb *per se* was not detected in any of the composite or single-serving samples. In composite sample detects, the sulfoxide constituted 79% of the total residue, while the sulfone constituted 21% of the total residue; results for single tubers were similar, with contributions of 78% and 22% for the sulfoxide and sulfone, respectively. The highest combined detected residue was in a single serving sample (i.e., one tuber), at 0.402325 ppm (or 0.3994 ppm, assuming an aldicarb *per se* residue of 0 ppm). For samples with detectable residues of the sulfoxide, the residue in the single serving varied from 0.1 to 7.4 times the corresponding composite residue. For the sulfone, single serving residues were 0.2 to 6.1 times the composite residue. The results of the study demonstrated the wide range in variability of individual tuber residues, relative to composite residues; variability for the sulfoxide was 1.5-4.7, while the sulfone variability was 2.1-4.9.

The Carbamate Task Force (CTF) also submitted a 1999 market basket survey which included single oranges collected in grocery stores and analyzed for aldicarb and metabolite residues.

In addition to the available monitoring data, extensive field trials have been conducted in which total and individual residues have been quantified in both composite and individual citrus fruits and potato tubers, including sweet potatoes. Many of these data are considered to be "farm gate" monitoring data; they do not reflect the worst-case conditions of field trials, but are not as close to the point of consumption as warehouse or supermarket-level monitoring data. In the "farm gate" monitoring data generated by the registrant and various food processors, most of the analyzed commodities were known to have been treated.

4.2.2 Dietary Exposure

An aldicarb acute dietary exposure assessment was conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™) software Version 2.0, which incorporates consumption data from USDA's Continuing Surveys of Food Intake by Individuals

(CSFII), 1994-96, 98. For risk assessment purposes the risk estimates were based on the human red blood cell cholinesterase depression endpoint. Results based on rat RBC and brain cholinesterase depression are provided for characterization purposes.

The aldicarb acute dietary exposure assessments were highly refined, incorporating monitoring and market basket survey data from the USDA/PDP (potatoes and sweet potatoes) and the CTF (oranges). These data sets were used to assess exposure from all potato and sweet potato food forms, as well as all citrus commodities and food forms (orange, grapefruit, lemon and lime).

In the 1997 PDP special survey, aldicarb and its metabolites were analyzed in 342 composite potato samples collected from states where aldicarb can be applied (FL, ID, OR and WA). Residues were detected in 20 composite samples, and individual potato tubers (10 per composite) from 16 of the composites with detects were analyzed. The highest combined residue in a composite sample was 0.17 ppm, which is below the reassessed tolerance of 0.2 ppm. The highest residue in an individual tuber was approximately 0.4 ppm, or twice the tolerance. Both the special survey and the composite potato data were used in the assessment. In the CTF market basket survey, aldicarb and metabolite residues were measured in 399 peeled oranges collected from grocery stores; residues were detected in 16 of the oranges sampled. The maximum orange residue of 0.03 ppm is 10 times lower than the reassessed tolerance of 0.3 ppm. In both the PDP and CTF studies, detected residues were the sulfone and sulfoxide metabolites, but aldicarb *per se* was not detected.

The PDP and CTF data were considered the best available data (for potatoes and citrus) for use in the dietary exposure assessments, since they reflect typical "dinner plate" exposures, and would not tend to significantly overestimate dietary exposure. For all other commodities, field trial data were used in the assessment, but residues were either very low or nondetectable (soybeans, cottonseed, peanuts, dry beans and coffee). Sugarbeet and sugarcane were excluded from the assessments, since aldicarb residues would not be expected in the processed commodities as consumed; the existing tolerance for sorghum was used in the assessment, but did not contribute to estimated dietary exposure due to the low %CT, the low tolerance, and the low consumption.

The most recent aldicarb use data and %CT estimates provided in the 12/99 and 5/00 Quantitative Usage Analyses (QUA) were incorporated into the preliminary dietary exposure analyses. Differences in %CT estimates for fresh vs. processed potatoes, oranges and grapefruit were included in the dietary exposure analyses. In addition, extensive processing/cooking data, generally indicating reduction of residues through boiling and juicing, were incorporated into the assessment. For potatoes, processing factors of 0.3X, 0.6X and 0.5X were used for dried, fried and boiled/cooked potatoes, respectively. Since aldicarb is systemic, typical home preparation practices such as washing and peeling would not significantly reduce residues.

4.2.2.1 Acute Dietary Exposure

Table 7 presents risk estimates calculated based on rat RBC ChEI, rat brain ChEI and human RBC ChEI. HED considers the human data to be the most appropriate for risk assessment purposes since the data directly measure the endpoint of concern in humans, rather than extrapolating from animal data. Risk estimates for all three endpoints are presented only to provide a more broad characterization of risks. The analysis which included existing aldicarb registrations indicates estimated acute dietary exposure and risk do not exceed HED's level of concern [i.e., >100 % of the acute population adjusted dose (aPAD)] for the general US population and relevant population subgroups at the 99.9th %ile of exposure. The estimated dietary exposure and risk for the general U.S. population at the 99.9th percentile exposure using the human RBC ChEI endpoint was 0.000280 mg/kg/day, or 37% aPAD. For children 1 – 2 years old, the most highly exposed population subgroup, dietary exposure was 0.000592 mg/kg/day, or 78% aPAD. If the PAD is based on the rat RBC or brain ChEI endpoint, risk estimates for children 1-2 years old were 102% and 68%, respectively.

An analysis was conducted to determine the foods or food forms which contribute the most to the exposure estimates. For all population subgroups, residues in potatoes were the most significant source of dietary exposure. For all infants, residues in sweet potato were also significant contributors. Citrus was also a notable contributor to the exposure estimates.

Sensitivity analyses were conducted to determine if assumptions for nondetectable residues overestimated exposures. These analyses consisted of (1) assuming aldicarb *per se* residues were 0 ppm; and (2) assuming nondetect residues in citrus monitoring samples were true zeroes. The sensitivity analyses indicated that these assumptions did not significantly impact the estimated exposure and risk for any of the population subgroups. These analyses indicate that actual detected residues from monitoring data were the source of the exposure and risk at the higher percentiles of exposure, and not assumed residues for nondetects (\leq LOD) (Table 8a). For the general US population, assuming aldicarb residues of 0 ppm and zero residues for nondetects in citrus, the estimated exposure was reduced from 37 to 36 % of the aPAD; for children 1-2 years old, the estimated exposure was reduced from 78 to 76 % of the aPAD.

Since residues in citrus and potatoes were identified as significant contributors to estimated dietary exposure, analyses were conducted in which citrus and potato commodities were separately omitted from the exposure assessment (Table 8b). When citrus commodities were excluded, estimated exposure for children 1-2 years old was reduced from 78% to 73% of the aPAD; while exposures for the general US population and all other population subgroups ranged from 29-59% of the aPAD. When potato commodities were excluded, the highest estimated exposure was for children 1-2, at 0.000211 mg/kg/day, or 28% of the aPAD; estimated exposures for all other population subgroups ranged from 4 to 22% of the aPAD, all based on human RBC ChEI. The comparative risk estimates based on rat RBC and brain ChEI endpoints are also shown in the summary tables.

More detailed information about these assessments can be found in the document titled *Aldicarb Revised Anticipated Residues and Dietary Exposure Analyses for the HED Human Health Risk Assessment* dated October 31, 2006.

4.2.2.2 Chronic Dietary

A chronic assessment was not conducted because the toxicity database for aldicarb indicates that the magnitude of ChEI does not increase with continued exposure, due to the reversibility of ChEI (generally within 24 hours). The longer-term exposures could be considered as a series of acute exposures.

Table 7. Aldicarb Acute (Food Only) Dietary Exposure and Risk (99.9 th % ile) – Existing Registrations				
Population	Exposure (mg/kg/day)	Human (RBC ChEI) %PAD	Rat (RBC ChEI) %PAD	Rat (Brain ChEI) %PAD
U.S. Pop	0.000280	37	48	32
All Infants	0.000312	41	54	36
Children 1-2 years	0.000592	78	102	68
Children 3-5 years	0.000480	64	83	55
Children 6-12 years	0.000351	46	60	40
Youth 13-19	0.000237	31	41	27
Adults 20-49 yrs:	0.000231	31	40	26
Adults 50+	0.000256	34	44	29
Females 13-49	0.000226	30	39	26

PAD = 0.00065 mg/kg/day Human (RBC ChEI); 0.00075 mg/kg/day Rat (Brain ChEI); 0.0005 mg/kg/day Rat (RBC ChEI)

Table 8a. Sensitivity Analysis - Aldicarb Acute Dietary Exposure and Risk (99.9 th % ile) – (Aldicarb = 0; citrus nondetects = 0)				
Population	Exposure (mg/kg/day)	Human (RBC ChEI) %PAD	Rat (RBC ChEI) %PAD	Rat (Brain ChEI) %PAD
U.S. Pop	0.000272	36	47	31
All Infants	0.000250	33	43	29
Children 1-2 years	0.000575	76	99	66
Children 3-5 years	0.000466	62	80	53
Children 6-12 years	0.000340	45	58	39
Youth 13-19	0.000230	30	40	26
Adults 20-49 yrs:	0.000224	29	39	26
Adults 50+	0.000251	34	43	29
Females13-49	0.000220	29	38	25

1. In citrus and potato commodities, aldicarb *per se* residues were assumed to be 0 ppm; in citrus commodities,
2. All nondetectable residues were assumed to be 0 ppm.

Table 8b. Aldicarb Sensitivity Analysis								
Population	No citrus				No potatoes			
	Exposure	Human (RBC ChEI)	Rat (RBC ChEI)	Rat(Brain ChEI)	Exposure	Human (RBC ChEI)	Rat (RBC ChEI)	Rat(Brain ChEI)
U.S. Pop	0.000266	35	46	31	0.000067	9	12	8
All Infants	0.000310	41	53	36	0.000034	4	6	4
Children 1-2 years	0.000555	73	95	64	0.000211	28	36	24
Children 3-5 years	0.000445	59	77	51	0.000169	22	29	19
Children 6-12 years	0.000343	46	59	39	0.000106	14	18	12
Youth 13-19	0.000232	31	40	27	0.000071	9	12	8
Adults 20-49 yrs:	0.000223	29	38	26	0.000051	7	9	6
Adults 50+	0.000250	34	43	29	0.000053	7	9	6
Females13-49	0.000220	29	38	25	0.000056	7	10	6

PAD = 0.00065 mg/kg/day Human (RBC ChEI); 0.0005 mg/kg/day Rat (RBC ChEI); 0.00075 mg/kg/day Rat (Brain ChEI)

4.3 Water Exposure/Risk Pathway

In accordance with the requirements of FQPA, HED human health risk assessments must consider the potential for exposure to pesticides in drinking water. The Environmental Fate and Effects Division (EFED/OPP) has completed a drinking water assessment for the aldicarb RED [N. Thurman, and J. Angier, 10/23/06, D333309]. The potential for aldicarb to reach and contaminate ground water was discovered in 1979, when high residues were detected in ground water on Long Island, NY. Concerns for aldicarb in ground water prompted the Agency to place aldicarb in Special Review status.

4.3.1 Environmental Fate Properties

The environmental fate database for aldicarb and its primary degradates, aldicarb sulfoxide and aldicarb sulfone, is incomplete. However, sufficient information is available to characterize the potential for aldicarb and its degradates to reach and persist in ground and surface water sources of drinking water.

Total aldicarb residues (i.e., aldicarb plus the sulfoxide and sulfone transformation products) are persistent and mobile in most soil types. The environmental profile is similar to that observed in plants, which consists of rapid oxidation of the parent aldicarb to aldicarb sulfoxide and sulfone, followed by breakdown (largely through hydrolysis) to the relatively non-toxic non-carbamate residues. The sulfoxide and sulfone are more soluble in water than the parent, aldicarb.

Aldicarb degradates readily leach to ground water when aldicarb is applied in areas with permeable (sandy) soil, significant rainfall, and shallow water tables. The vast amount of ground water monitoring data demonstrates that once aldicarb residues reach ground water, they degrade very slowly. Temperature is a significant factor in controlling aldicarb degradation in ground water, and increased persistence is observed in cooler northern climates. However, most community ground water supplies are from deeper, confined aquifers that would not likely be contaminated with aldicarb residues. Therefore, people most likely to be exposed to aldicarb residues in drinking water are those who have private (domestic) wells in vulnerable aldicarb use areas.

Surface water monitoring data for aldicarb and its metabolites are limited, especially when compared with the quantity of ground water monitoring data. Aldicarb residues have not been detected frequently or in high amounts in surface water in the USGS NAWQA monitoring. While the NAWQA monitoring sites are not targeted to aldicarb use areas and the frequency of sampling is not designed to capture peak concentrations in surface water, the results suggest that actual concentrations of aldicarb residues in surface water are likely to be closer to the single or sub-parts per billion range than to 10-30 ppb.

Although previous drinking water (from groundwater sources) exposure assessments for aldicarb relied on a summary of available monitoring data, the vast majority of the monitoring represents unknown conditions (in particular, no information on aldicarb rates, distances between fields and wells, ground water depth, type of well, soil or hydrogeologic conditions, or ground water pH)

and represented monitoring prior to label changes. Bayer CropScience has recently submitted a compilation of recent monitoring of private wells in selected areas of the US. Although EPA has not yet had time to fully evaluate the monitoring (in particular, the correlation of aldicarb detects with high leaching potential soils, distance between field and well, depth to ground water, and nature of well), a brief review of study results indicates that the estimated exposures reported below are on the same order as reported detections.

EPA promulgated a final National Primary Drinking Water Regulation for aldicarb, aldicarb sulfoxide, and aldicarb sulfone on July 1, 1991. EPA set the maximum contaminant level goal (MCLG, a non-enforceable health goal that is used as the target for enforceable Maximum Contaminant Levels, or MCLs) at 0.001 part per billion (ppb) and MCLs of 0.003 ppb for aldicarb, 0.004 ppb for aldicarb sulfoxide, and 0.002 ppb for aldicarb sulfone. In response to an administrative petition from the manufacturer and primary data-doer, the Agency issued an administrative stay of the effective date of the MCLs; i.e., the MCLs never became effective.

The Agency issued an updated drinking water health advisory in 1995. Health advisories serve as informal technical guidance to assist officials responsible for protecting public health (e.g., spills or contamination) but are not enforceable federal standards.

4.3.2 Estimated Environmental Concentrations (EECs)

Surface Water

The revised surface water exposure assessment focused on three high aldicarb use/ exposure scenarios: Florida citrus (central FL), Louisiana/Mississippi cotton, and North Carolina peanuts/cotton. While these scenarios were selected based on combined N-methyl carbamate uses in the vicinity of drinking water intakes in relatively high runoff potential areas, they represent areas of relatively high aldicarb use. Thus, the scenarios represent drinking water intakes with relatively high potential for aldicarb exposure.

Region-specific typical application rates were used. These rates, along with the number of applications are less than the maximum label rates. While typical rates, representing an “average” of high and low pest pressures over time, might be reflective of ground water exposures, in which the length of time for transport from the surface to groundwater tends to lessen the variability in concentrations over time, they are more likely to underestimate surface water concentrations in the case of maximum use in response to high pest pressures. Likewise, they will likely overestimate surface water concentrations in the case of low pest pressures. Table 9 summarizes the distributions of total aldicarb residues for various scenarios, reflecting the relative contributions of aldicarb from multiple crop uses in the watershed.

Table 9: Estimated concentrations of total aldicarb residues in surface water sources of drinking water in high runoff potential areas based on typical rates.							
Scenario Location	Crops	Concentrations, ug/l					
		Max-imum	99 th %ile	95 th %ile	90 th %ile	80 th %ile	75 th %ile
FL central ridge citrus	Oranges	9.6	1.5	0.24	0.08	0.014	0.007
	Grapefruit	0.6	0.1	0.02	0.005	0.001	0.0005
	Aggregate	10.2	1.6	0.26	0.85	0.015	0.007
NC Coastal Plain	Cotton	4.5	1.0	0.14	0.04	0.004	0.001
	Peanuts	0.8	0.1	0.03	0.01	0.001	<0.001
	Aggregate	4.6	1.0	0.19	0.08	0.01	0.005
LA/MS Mid-south	Cotton	0.8	0.2	0.02	0.004	<0.001	<0.001

Ground Water

EPA used the Pesticide Root Zone Model (PRZM) to simulate transport processes through high leaching potential soils to a shallow unconfined aquifer with a water table at 30 feet (approximately 9 m) below the surface.

Table 10 summarizes the distributions of total aldicarb residues for various scenarios and varying well setback distances. These distributions of total aldicarb residues (parent plus the sulfoxide and sulfone transformation products) represent 25 years of simulations in ground water and reflect shallow (30-ft) private wells; high leaching potential soils, aldicarb applications to fields at label setback distances between the field of application and the well, as specified on the current aldicarb label; a high-end typical lateral flow velocity to estimate the travel time from the field of application to the well based on well setback distance; typical application rates for aldicarb, provided by the Biological and Economic Analysis Division (BEAD); and acidic soil and ground water, which favor the persistence of the sulfoxide and sulfone transformation products (both degrade rapidly under alkaline conditions; the parent aldicarb is less susceptible to alkaline hydrolysis). The distributions highlighted in bold in the table represent estimated residues for the labeled setback distance between the treated field and the well. The 0-foot “setback” estimates in-field concentrations which were used to compare model estimates with in-field ground water monitoring data.

The ground water exposure represents private drinking water wells. EFED assumed in this assessment that, in general, public water supplies supplied by ground water will typically draw from deeper aquifers and/or aquifers that have a relatively impermeable layer between the surface and the water supply. Such supplies are expected to be much less vulnerable to pesticide contamination. Public water supplies have a higher probability of being treated, although conventional treatments processes are likely to result in little or no reduction of aldicarb residues in water. However, where lime softening, which will accelerate pH-dependent hydrolysis for aldicarb sulfoxide and sulfone, or activated carbon filtration is used, some reduction in aldicarb residues between untreated and treated water may occur.

Table 10: Estimated concentrations of total aldicarb residues in private, shallow (30-ft) wells. Concentrations represent typical application rates in high leaching potential soils.

Scenario	Well setback	Concentrations, ug/l						
		Maximum	99 th %ile	95 th %ile	90 th %ile	80 th %ile	75 th %ile	50 th %ile
FL Central Ridge/ Citrus	0 ft	58.5	55.5	50.9	48.5	41.8	40.3	33.8
	300 ft	24.9	23.6	21.6	20.6	17.8	17.2	14.4
	1000 ft	3.0	2.8	2.6	2.4	2.1	2.0	1.7
FL Potatoes (alkaline GW)	0 ft	3.9e-05	3.0e-05	1.9e-05	1.3e-05	8.1e-06	6.2e-06	2.3e-06
	300 ft	1.7e-05	1.3e-05	8.0e-06	5.7e-06	3.5e-06	2.7e-06	9.9e-07
GA Coastal Plain Peanuts/ cotton	0 ft	15.2	14.1	12.0	11.2	10.1	9.6	7.2
	300 ft	6.5	6.0	5.1	4.8	4.3	4.1	3.1
	500 ft	3.7	3.4	2.9	2.7	2.5	2.4	1.8
	1000 ft	0.9	0.8	0.7	0.7	0.6	0.6	0.4
NC Coastal Plain Peanuts/ cotton	0 ft	3.1	2.9	2.5	2.3	2.0	2.0	1.5
	300 ft	1.3	1.2	1.1	1.0	0.9	0.8	0.6
	500 ft	0.8	0.7	0.6	0.6	0.5	0.5	0.4
	1000 ft	0.2	0.2	0.2	0.1	0.1	0.1	0.1
WA Potato (alkaline soil, GW)	300 ft, 15-ft depth	0.001	0.001	<0.001	<0.001	<0.001	<0.001	<0.001

4.4 Residential Exposure/Risk Pathway

No aldicarb products are intended for sale to homeowners or for use by professional applicators in residential environments. In addition, the potential for off-target migration of aldicarb during agricultural applications is minimal, due to the physical characteristics of the products (all granular formulations) and the requirement for soil incorporation at treatment. Therefore, no residential exposure/risk assessment has been completed in conjunction with the agricultural uses for aldicarb. However, an inhalation risk assessment for adult smokers has been completed since aldicarb is registered for use on tobacco.

In assessing exposure through use of tobacco, HED has assumed that the greatest exposure to aldicarb would come from cigarettes. Further, HED has assumed that the average U.S. smoker smokes 15 cigarettes per day [Pierce, J. P., et al. 1989. *Tobacco Use in 1986 - Methods and Basic Tabulations from Adult Use of Tobacco Survey*. U.S. Dept. of Health and Human Services Publication Number OM90-2004. Office on Smoking and Health, Rockville, Maryland.].

Residue data submitted to support aldicarb use on tobacco were reviewed in the Residue Chemistry Chapter of the Aldicarb Reg. Std. (11/18/83). These data are considered adequate for the purpose of assessing human exposure to aldicarb residues in cigarette smoke.

In a greenhouse study, [¹⁴C]aldicarb was applied close to the 1X rate, and residues were measured in green leaves, flue-cured leaves, and in smoke. Residues in smoke were 0.5 ppm, consisting of aldicarb sulfone (0.3 ppm) and aldicarb sulfoxide (0.2 ppm). Total [¹⁴C]aldicarb

residues in leaves from the greenhouse study were higher than those reported in a field study. Smoke residues were not determined using leaves from the field study. Therefore, for the purpose of this exposure assessment, aldicarb residues in tobacco smoke were assumed to be 0.5 ppm; this is considered to be an overestimate of potential residues in smoke, based on the higher residues in leaves from the greenhouse study.

In assessing exposure to aldicarb from tobacco, HED has assumed that 100% of the aldicarb inhaled in the smoke is absorbed (i.e., that none of the residue is exhaled along with the smoke). This results in an overestimate of actual likely exposure. Assuming a smoke residue level of 0.5 ppm, a smoking frequency of 15 cigarettes per day, and assuming an average body weight of either 60 kg (females) or 70 kg (general adult population), HED estimates that exposure to aldicarb will not exceed 0.000107 mg/kg/day for the general adult population [$0.5 \mu\text{g/g cigarette} \times 1 \text{ g/cigarette} \times 15 \text{ cigarettes/day} \times 1 \text{ mg}/1000\mu\text{g} \div 70 \text{ kg body weight} = 0.000107 \text{ mg/kg/day}$] and 0.000125 mg/kg/day for females (60 kg body weight).

The Margin of Exposure (MOE) is a measure of the estimated exposure with respect to the Agency's level of concern, usually the NOAEL. The MOE is expressed as a ratio of the NOAEL (or LOAEL) to the estimated exposure; the higher the MOE, the lower the risk. The target MOE for aldicarb is 20 i.e., 10X (intraspecies) and 2X (interspecies); estimated MOEs less than 20 represent a risk concern. Using the inhalation BMDL₁₀ of 0.013 mg/kg/day, the acute MOE for aldicarb exposure from the use of tobacco is estimated to be 104 for females, and 121 for males. These MOEs are greater than the target MOE of 20, indicating that exposure and risk from aldicarb residues in tobacco are not of concern. These estimates are considered to be very conservative assumptions with respect to residues in tobacco, and may overestimate exposure through this route.

5.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATIONS

In accordance with FQPA, HED must consider and aggregate pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

Since there is no potential for exposure to aldicarb and metabolites in residential settings, aggregate exposure and risk assessments include only dietary food and water sources of exposure, and are limited to acute and chronic durations. Chronic exposure to aldicarb is considered to be a series of acute exposures, and a separate chronic assessment is not necessary; therefore, the aggregate dietary exposure (food plus water) can be compared to the acute PAD to determine the risk associated with the estimated exposures (see Hazard Profile, Section 3.1 for rationale concerning need for a chronic assessment.) Per Agency policy, tobacco use is not included in aggregate assessments.

Exposure and risk estimates from food alone were described in Section 4.2 of this document. A distribution of estimates of possible concentrations in drinking water was used in the dietary assessment. Approximately 11,000 values were generated based on typical aldicarb use patterns. The values were not adjusted for percent crop area (PCA). These values represent the complete daily 36 year PRZM-EXAMS (surface water) and 25 year PRZM (groundwater) output distribution. A RDF file was created using these values for the two commodities “Water, direct, all sources” and “Water, indirect, all sources” in the residue file editor for DEEM-FCID.

5.1 Acute Aggregate Risk Assessment [Food plus Drinking Water from Surface Water Sources]

The surface water concentrations used were provided by the Environmental Fate and Effects Division (Nelson Thurmon and Jonathon Angier) and are from a PRZM-EXAMS analysis. The aldicarb distributions were generated for 3 regions which represent high aldicarb use areas - Florida citrus, North Carolina peanuts/cotton, and Louisiana/Mississippi cotton. The results from this analysis have been characterized as somewhat conservative, but it is possible that occasionally these levels of residue concentrations may be found. Results of these assessments are shown in Table 11.

Table. 11. Aldicarb Acute Aggregate Exposure and Risk for Select Population Subgroups at the 99.9th %ile of Exposure [Based on Surface Water Concentrations from Modeling]								
Regions	U.S. Population		All infants		Children 1-2 years		Females 13-49	
	Exposure	%PAD	Exposure	%PAD	Exposure	%PAD	Exposure	%PAD
Human - RBC								
Florida	0.000273	42	0.000579	89	0.000532	82	0.000231	36
North Carolina	0.000246	38	0.00036	55	0.000505	78	0.0002	31
Mississippi	0.000239	37	0.000267	41	0.000501	77	0.000194	30
Rat – RBC								
Florida	0.000273	55	0.000579	116	0.000532	107	0.000231	46
North Carolina	0.000246	49	0.00036	72	0.000505	101	0.0002	40
Mississippi	0.000239	48	0.000267	53	0.000501	100	0.000194	67
Rat – Brain								
Florida	0.000273	36	0.000579	77	0.000532	71	0.000231	31
North Carolina	0.000246	33	0.00036	48	0.000505	67	0.0002	27
Mississippi	0.000239	32	0.000267	36	0.000501	67	0.000194	55

1. EDWCs were based on the following scenarios: Mississippi/Louisiana Cotton; North Carolina Peanut/Cotton; Florida Citrus
2. Generated using the DEEM-FCID model - Version 2.03
3. Acute Aggregate Risk = % of the aPAD= [(Total Exposure/aPAD mg/kg/day) x 100]

The acute aggregate risk estimates when food and drinking water from surface water sources are assessed show HED's level of concern is not exceeded (<100% aPAD). The most highly exposed population subgroup was infants at 89% aPAD at the 99.9th percentile when compared to the human RBC endpoint.

5.2 Acute Aggregate Risk Assessment [Food plus Drinking Water from Ground Water Sources]

An aggregate assessment was also conducted combining food with ground water sources of drinking water as described in the above Section 5.0. The estimated drinking water concentrations were obtained from PRZM Modeling. The drinking water estimates were based on the three most vulnerable regions of the United States and incorporates well setbacks ranging from 300 to 1000 feet. Using the DEEM dietary model alone, the data indicate that aggregate exposure from food and ground water sources of drinking water exceeds 100% aPAD for some regions including Florida which has a well setback of 1000 feet. Risk estimates ranged from 80 to 145% of the aPAD for children 1-2 years old and 53 to 285% of the aPAD for infants (<1 years old). Acute aggregate exposure and risk estimates (food and drinking water from groundwater sources) for the general population, all infants, children 1-2., and females 13-49 years are shown in Table 12. These are overestimates of actual risks since the food diaries used by Dietary Exposure Evaluation Model-Food Consumption Intake Database (DEEM-FCID Version 2.03) are based on total daily intake. The estimated risks are overestimates to the extent that food and drinking water are consumed throughout the day, rather than during only one event and there is regeneration of cholinesterase between eating and drinking events.

HED further refined the acute aggregate risk from food and groundwater by incorporating the time and amounts consumed for each eating occasion from the USDA CSFII food diaries to estimate exposures and risks on each eating occasion throughout the day. This refined assessment also incorporated the available toxicological data which indicates that the estimated half-life for cholinesterase inhibition resulting from aldicarb exposure is 2-hours or less. Exposures and risks using this approach were calculated using the DEEM model coupled to a SAS[®] program which accounted for cholinesterase regeneration. To verify these DEEM-based eating occasion results, the Agency's Office of Research and Development's Stochastic Human Exposure and Dose Simulation (SHEDS) model was also used to conduct an eating occasion analyses for aldicarb. The SHEDS eating occasion results are similar to the DEEM-based results, providing additional assurance regarding the accuracy of these computations. SHEDS was also used to conduct further sensitivity analyses on the half-life parameter, as well as addressing issues regarding both direct and indirect drinking water consumption. Detailed information on the methods used to derive the aggregate exposures are presented in the document titled "Aldicarb: Acute Dietary Exposure Assessment to Support the Reregistration Eligibility Decision" [S. Nako and J. Xue, 11/01/06].

Table 13 presents the respective DEEM-FCID[®] and SHEDS[®], estimated risks at the per capita 99.9th percentile using a 2 hour half-life for cholinesterase inhibition. These eating occasion results are based on several major assumptions: (i) 2 hour half-life, (ii) allocation of direct drinking water consumption based on 6 equal and fixed occasions, and (iii) no modifications to the amount of indirect drinking water consumed as reported in the CSFII diaries for infants. Direct water is water that is consumed from the tap and indirect water is considered water that is used in the preparation of food. For food only, these levels are below the level of concern for all subpopulations (Table 7). Four drinking water scenarios were modeled for aldicarb from groundwater sources: 3 ground water scenarios for aldicarb use on peanuts/cotton in Georgia with an assumption of 300 ft, 500 ft and 1000 ft well set backs, and one ground water scenario for aldicarb use on Florida citrus with a 1000 ft setback. The estimated risks at the per capita 99.9th percentile are below the level of concern for all four scenarios, for all subpopulations except for infants. For infants, the estimated risks at the per capita 99.9th percentile exceeds the level of concern under the Georgia 300 ft scenario (139% - 147% of the aPAD).

It should be noted that incorporating eating occasion analysis and the 2 hr. recovery half life for aldicarb into the *Food Only* analysis does not significantly change the risk estimates when compared to baseline levels (for which a total *daily* consumption basis – and not eating occasion - was used) From this, it is apparent that modifying the analysis such that information on eating occasions and aldicarb half life is incorporated results in only minor reductions in estimated risk: generally on the order of several percent, at most, for all age groups. However, risk estimates for which food and drinking water are jointly considered and incorporated are reduced considerably (by a factor of 2 or more in some cases) compared to baseline and is not unexpected: infants receive much of their exposures from indirect drinking water in the form of water used to prepare infant formula.

**Table. 12. Aldicarb Acute Aggregate (Food plus Water) Exposure and Risk for Select Population Subgroups at the 99.9th %ile of Exposure.
[Based on Ground Water Concentrations from Modeling]**

Region ¹	Well Setback (ft)	Gen Population		All Infants (<1 Year)		Children (1 -2 Years)		Females 13-49 Years	
		Exp. (mg/kg/day) ²	%aPAD ³	Exp. (mg/kg/day) ²	%aPAD ³	Water Exp. (mg/kg/day) ²	%aPAD ³	Water Exp. (mg/kg/day) ²	%aPAD ³
Human RBC									
Coastal Plain: southern GA peanuts/cotton	300 ft	0.000774	119	0.001853	285	0.000943	145	0.000595	92
Coastal Plain: southern GA peanuts/cotton	500 ft	0.000482	74	0.001089	168	0.000636	98	0.000370	57
Coastal Plain: southern GA peanuts/cotton	1000 ft	0.000255	39	0.000346	53	0.000519	80	0.000205	31
FL/Central Ridge Citrus	1000 ft	0.000444	68	0.001000	154	0.000598	92	0.000340	52
Coastal Plain: eastern NC peanuts/cotton	300 ft	0.000273	42	0.000460	71	0.000526	81	0.000217	33
Rat - RBC									
Coastal Plain: southern GA peanuts/cotton	300 ft	0.000774	155	0.001853	371	0.000943	189	0.000595	175
Coastal Plain: southern GA peanuts/cotton	500 ft	0.000482	96	0.001089	218	0.000636	127	0.000370	74
Coastal Plain: southern GA peanuts/cotton	1000 ft	0.000255	51	0.000346	69	0.000519	104	0.000205	41
FL/Central Ridge Citrus	1000 ft	0.000444	89	0.001000	200	0.000598	120	0.000340	115
Coastal Plain: eastern NC peanuts/cotton	300 ft	0.000273	55	0.000460	92	0.000526	105	0.000217	43
Rat - Brain									
Coastal Plain: southern GA peanuts/cotton	300 ft	0.000774	103	0.001853	247	0.000943	126	0.000595	117
Coastal Plain: southern GA peanuts/cotton	500 ft	0.000482	64	0.001089	145	0.000636	85	0.000370	49
Coastal Plain: southern GA peanuts/cotton	1000 ft	0.000255	34	0.000346	46	0.000519	69	0.000205	27
FL/Central Ridge Citrus	1000 ft	0.000444	59	0.001000	133	0.000598	80	0.000340	45
Coastal Plain: eastern NC peanuts/cotton	300 ft	0.000273	36	0.000460	61	0.000526	70	0.000217	29

Table 13. Aldicarb Acute Aggregate (Food plus Drinking Water from Groundwater Sources) Risks Assuming 2-hour Half Life for Cholinesterase-Inhibition (per capita, 99.9th percentile exposure)

Subpopulation	DEEM-Based Eating Occasion				
	Food Only	GA-GW 300 ft	GA-GW 500 ft	GA-GW 1000 ft	FL-SW 1000 ft
USPop	34%	58%	44%	36%	42%
All Infants	41%	147%	88%	43%	80%
Children 1-2 yrs	72%	95%	80%	76%	78%
Children 3-5 yrs	60%	77%	64%	59%	62%
Children 6-12 yrs	46%	48%	45%	42%	44%
Youth 13-19 yrs	28%	46%	33%	28%	30%
Adults 20-49 yrs	29%	54%	38%	30%	36%
Adults 50+ yrs	34%	47%	37%	34%	37%
Females 13-49 yrs	29%	50%	35%	28%	34%
Subpopulation	SHEDS-NMC Eating Occasion				
	Food Only	GA-GW 300 ft	GA-GW 500 ft	GA-GW 1000 ft	FL-SW 1000 ft
USPop	35%	55%	42%	36%	41%
All Infants	41%	139%	85%	42%	77%
Children 1-2 yrs	77%	91%	80%	78%	79%
Children 3-5 yrs	57%	71%	61%	57%	60%
Children 6-12 yrs	43%	46%	44%	43%	44%
Youth 13-19 yrs	31%	44%	34%	31%	33%
Adults 20-49 yrs	30%	52%	37%	30%	36%
Adults 50+ yrs	32%	45%	36%	33%	35%
Females 13-49 yrs	30%	50%	37%	30%	36%

5.3 Chronic Aggregate Risk Assessment

A chronic aggregate assessment was not conducted because the toxicity database for aldicarb indicates that the magnitude of ChEI does not increase with continued exposure, due to the reversibility of ChEI (generally within 8 to 24 hours) exhibited by aldicarb and other carbamate pesticides. The longer-term exposures could be considered as a series of acute exposures.

6.0 CUMULATIVE RISK

The Food Quality Protection Act (1996) stipulates that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk posed by the chemical on, among other things, available information concerning the cumulative effects to human health that may result from dietary, residential, or other non-occupational exposure to other substances that have a common mechanism of toxicity. The reason for

consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. A person exposed to a pesticide at a level that is considered safe may in fact experience harm if that person is also exposed to other substances that cause a common toxic effect by a mechanism common with that of the subject pesticide, even if the individual exposure levels to the other substances are also considered safe.

The Agency has determined that N-methyl carbamate pesticides should be considered as a Common Mechanism Group due to their ability to inhibit acetylcholinesterase. A cumulative risk assessment for this Common Mechanism Group, which includes aldicarb, will be available later this year. This human health risk assessment for aldicarb does not include cumulative exposures or risks from other N-methyl carbamate pesticides.

7.0 OCCUPATIONAL EXPOSURE

The HED occupational exposure and risk assessment for aldicarb is based on a limited number of occupational exposure scenarios, or categories of exposures, derived from the uses described on registered labels. HED risk assessments typically consider several types of potentially exposed populations including: handlers who are those involved in the pesticide application process (e.g., mixer/loaders or applicators) and post-application workers or those who can be exposed by working in environments that have been previously treated. The aldicarb use pattern indicates that routine exposures are expected for occupational handlers, including loaders and applicators. Due to the application timing and the requirement for soil incorporation of aldicarb granules, postapplication exposures are not generally expected; hence, a postapplication exposure assessment was not conducted. Section 7.1 presents the results of the risk assessment for aldicarb handlers while Section 7.2 describes the lack of potential for post-application exposures.

Since the toxicological endpoints for aldicarb dermal and inhalation risk assessments were the same (RBC cholinesterase inhibition), risks were expressed in terms of combined dermal and inhalation MOEs. In addition, the same studies were used to assess risks for all pertinent exposure durations; therefore, risk estimates do not vary with the duration of exposure.

A summary of the use pattern and formulation information for occupational risk assessment is provided in Table 14.

Table 14. Aldicarb Use Pattern/Formulation Information Relevant to Occupational Exposure Assessment.					
Formulation Type	Application Equipment (Loader/Applicator)	Use Sites	Appl. Rate Range	Application Frequency	Average Appl. Rates
Terrestrial Crops					
15G	Solid broadcast spreader	Tree fruit/ Nut crops	Pecans: 2.6 to 10.1 lb ai/A/season Citrus: 5 lb ai/A Coffee: 0.11 oz/tree [4.4 lb ai/A/season]	Pecans: 1 or 2x/season Citrus: 1x/Season Coffee: 2x/Season	1.4 - 3.8 lb ai/A/year
15G	Solid broadcast spreader	Field/forage fiber/small fruit/veg.	Beans: 1.1 - 2.1 lb ai/A; Cotton: 0.75 - 4.1 lb ai/A; Peanuts/Potatoes/ Soybeans/Sugarcane/ Sweet potatoes: 3 lb ai/A; Sorghum: 1.1 lb ai/A; Sugar beets: 2.1-5 lb ai/A	3x/season (max.); typically 1 or 2x/season	0.6 - 2.7 lb ai/A/year
15G	Solid broadcast spreader	Non-Food/Feed	Tobacco: 3 lb ai/A	1x/season	1.6 lb ai/A/year
Ornamental Crops					
10G	Solid broadcast spreader	Ornamentals	5 lb ai/A	no data	no data

7.1 Handler

The aldicarb use pattern results in a limited number of occupational handler scenarios: (1) loading granules; and (2) applying granules using a solid broadcast spreader. Loading activities can involve both open loading (i.e., with typical bags) or the use of closed Lock-n-Load systems. Application activities can also involve open or closed cab tractors. These two scenarios were assessed using exposures derived from a formulation- and chemical-specific study that monitored open loading and open-cab application conducted by the registrant (MRID 438525-01), the PHED (Pesticide Handlers Exposure Database), and a study which monitored granular closed loading and closed cab application in conjunction with high levels of personal protective equipment (i.e., MRID 447933-01 which was conducted using terbufos, data compensation issues may apply; this study was considered for comparative purposes based on comments from Bayer Crop Sciences). The two studies can be identified by the following citations:

- **Worker Loader and Applicator Exposure to Temik 15G.** Study number 94388, Unpublished study prepared by ABC Laboratories, Pan-Ag Division; Rhone-Poulenc Ag Company, **EPA MRID 43852501**: Rosenheck, L., Schuster, L. (1995).

- ***Exposure of Farmworkers To Terbufos (CL 92100) While Loading COUNTER 15G Systemic Insecticide-Nematicide With A Lock-N-Load Closed Handling System And Applying COUNTER 15G To Corn At Planting Time;*** (3/26/99) Authored by Joseph Higham; Completed by ABC Laboratories of Columbia MO, Agrisearch of Frederick MD, and American Cyanamid of Princeton NJ.; Project ID #s include: Exhibit 2 of EPA MRID 447933-01, Terbufos 99-02, EXA 99-004, EXA 99-006, and RES 99-003, Sponsored by American Cyanamid.

The formulation- and chemical-specific study (MRID 438525-01) used aldicarb low-dust granules which are the only commercially marketed products. This study provides the most representative open loading and open cab application exposure estimates for aldicarb because of the low friability of aldicarb-containing products based on how it is formulated. PHED data are available for this scenario, and would be used in lieu of MRID 438525-01 if not available, but it is not recommended because exposure estimates would be based on the use of more friable clay granules which create more dust and, hence, higher exposure levels which would not be realistically expected. Aldicarb is also marketed in Lock-n-Load closed loading systems and it can be applied using closed cab tractors. As such, these exposures were also considered in this assessment. The aldicarb-specific study (MRID 438525-01) did not quantify the exposures associated with the use of these types of engineering controls. Instead, both PHED and another study (MRID 447933-01) were used to evaluate exposures associated with closed loading systems and closed cab. The PHED-based values reflect normal work clothing and estimates from MRID 447933-01 reflect the use of aprons gloves for the loaders and coveralls and gloves for the applicators inside of a closed cab.

The following factors were also used to estimate handler exposure and risk, and are considered typical for HED handler assessments:

- Exposures were assessed for an 8-hour occupational workday.
- Daily acres treated/day assumptions were 80 acres for orchard and field crops; 50 acres for coffee plantations; and 10 acres for ornamentals.
- Risk estimates were calculated based on an endpoint identified in a human study which has been recently evaluated by the Agency's Human Studies Review Board and deemed appropriate for risk assessment. Additionally risks have been calculated for comparative purposes in an effort to provide additional characterization based on endpoints which were identified in rat data (i.e., red blood cell and brain cholinesterase inhibition).
- Exposures were based on maximum application rates for representative crops.
- The average body weight for an adult handler is 70 kg.

Estimated short- and intermediate-term risks (MOEs) are presented in Table 15 and were calculated based on each of the applicable endpoints which have been identified. Based on the human study endpoint and the aldicarb specific worker exposure data (MRID 438525-01), risks were not of concern for all open cab application and all but one open loading exposure scenarios (i.e., only the highest rate on pecans at 6 lb ai/acre for loaders was of concern with an MOE = 8.8 where no concern is ≥ 10). The same general trend was also observed based on the risks calculated using the rat-based endpoints. PHED and the terbufos study (MRID 447933-01 as identified in comments by Bayer Crop Science) were both used to assess the risks for those who

load and apply aldicarb using closed systems or closed cab tractors. The results for loaders using closed systems also indicated that risks were of not concern for most exposure scenarios regardless of which hazard endpoint was considered (i.e., human- or rat-based) but results did vary based on the source of the exposure data. No risks of concern for closed loaders were identified based on the use of the terbufos study which monitored individuals using actual closed loading systems. The PHED estimates were based on the use of a protection factor which should be considered in the interpretation of the results. In only a few instances for loaders using closed systems based on PHED were risks identified that were of potential concern. Loader risks based on the rat RBC endpoint (i.e., target MOEs = 14.4 & 17.5 for 80 acres at ~5+ lb ai/acre) and the human endpoint (i.e., MOE = 9.4 for 80 acres at 6 lb ai/acre) were just slightly below the risk targets (i.e., MOEs = 20 & 10, respectively). For applicators, no risks were identified based on the terbufos data which monitored individuals in closed cabs with wearing coveralls and gloves which represent more protective clothing than normally used in cabs. Based on PHED applicator data, the trend is very different in that risks were of concern for all scenarios considered (i.e., MOEs range from <1 to 8.2 where no concern is ≥ 10) based on the human study endpoint. The trend is similar based on the rat endpoints.

In the interpretation of the results of this assessment, several factors should be considered including:

- The aldicarb study (MRID 438525-01) which was used to address exposures for open loading and open cabs is formulation- and chemical-specific that mirrors how aldicarb is formulated, packaged, handled and used in agriculture; the terbufos study (MRID 447933-01) monitored individuals using engineering controls (i.e., closed loading and closed cab tractors) and there were no risks associated with these exposure estimates but risks were identified for closed cab applicators based on PHED; the PHED-based risks are not believed to be a significant issue for aldicarb because of the nature of the granular material as evidenced by the lack of risk concerns for open-loaders based on the aldicarb study and also the lack of risk concerns based on the terbufos study exposure estimates.
- The results of this assessment supersede those presented in the previous risk assessment D327738 (May 12, 2006) and the previous occupational and residential exposure chapter D311821 (January 11, 2005). The scenarios essentially remain the same but the major changes are that PHED estimates for engineering controls are now included and the hazard inputs have been modified so the key risk results are now based on the human study endpoint since the recent HSRB meeting.
- A dermal absorption factor of 100 percent has been used and if that factor changed, risks would also change proportionately.
- Current aldicarb labels require coveralls worn over shorts and short-sleeved shirts, chemical-resistant gloves, respirator, footwear, eyewear, and aprons for loaders. In MRID 4385250, subjects wore protective clothing similar to current label requirements including loaders who wore aprons. It should be noted that the PHED-based exposure

estimates do not reflect the use of aprons. It should also be noted that in the terbufos study (MRID 447933-01), loader protective clothing levels were similar to the label (except the subjects wore long pants instead of shorts) but applicator levels of protective clothing were higher than required for closed cab applicators since coveralls and gloves were worn during application in closed cabs. The use of additional protective clothing does not impact the overall results, however, because the margins of exposure are large compared to the target levels which indicates that even if coveralls and gloves were not worn it is anticipated that risks of concern would be unlikely because the cab structure itself is protective as are the low-friability granules themselves as evidenced by the low lack of risk concerns for open loading.

Table 15: Summary of Short-/Intermediate-Term Occupational Handler Noncancer Risks											
Scenario	Rate (lb ai/acre) & Crop	Area Treated (acres/day)	MOEs Based On MRID 438525-01 [Aldicarb-specific study] (Open bag/open cab tractor & label PPE)			MOEs Based On PHED For Engineering Controls (Closed loading & Closed cab tractor)			MOEs Based On MRID 447933-01 [Terbufos Engineering Control Study] (Closed loading & cabs, apron or coverall, gloves)		
			Based On Rat RBC Endpoint	Based On Rat Brain Endpoint	Based On Human Endpoint	Based On Rat RBC Endpoint	Based On Rat Brain Endpoint	Based On Human Endpoint	Based On Rat RBC Endpoint	Based On Rat Brain Endpoint	Based On Human Endpoint
Loaders											
1 Granular: Solid broadcast spreader	6 (pecans)	80	13.6	20.3	8.8	14.4	21.7	9.4	49	73	32
	4.95 (citrus)	80	16.4	24.7	10.7	17.5	26.3	11.4	59	89	38
	4.4 (coffee)	50	29.6	44.4	19.2	31.5	47.3	20.5	106	160	69
	3 (potato)	80	27.1	40.7	17.6	28.9	43.3	18.8	98	146	63
	3.15 (cotton)	80	25.8	38.8	16.8	27.5	41.3	17.9	93	139	60
	1.05 (sorghum)	80	77.5	116.3	50.4	82.5	123.8	53.6	279	417	181
	5 (ornamentals)	10	130.2	195.3	84.7	138.6	207.9	90.1	468	710	304
Applicators											
2 Solid broadcast spreader (granular)	6 (pecans)	80	33.8	50.6	21.9	1.3	2.0	0.9	78	117	51
	4.95 (citrus)	80	40.9	61.4	26.6	1.6	2.4	1.0	94	141	61
	4.4 (coffee)	50	73.7	110.5	47.9	2.9	4.3	1.9	170	254	110
	3 (potato)	80	67.5	101.3	43.9	2.6	3.9	1.7	155	233	101
	3.15 (cotton)	80	64.3	96.5	41.8	2.5	3.8	1.6	148	222	96
	1.05 (sorghum)	80	192.9	289.4	125.4	7.5	11.3	4.9	444	666	289
	5 (ornamentals)	10	324.1	486.1	210.6	12.6	18.9	8.2	746	1119	485
The required uncertainty factor which establishes a risk concern is 20 for the risks based on the rat endpoints and 10 for the risks based on the human endpoint. Based on the results of the recent HSRB meeting on aldicarb											
If MOEs are of concern and did not exceed the required uncertainty factor (i.e., target MOE) they are bolded.											

7.2. Incident Data

Incident data were obtained from reports submitted to the Incident Data System from 1996 through 1999. The scientific literature on aldicarb poisonings were reviewed with particular attention to the time from onset of symptoms to recovery, both with and without treatment, doses associated with symptoms of carbamate toxicity and sensitivity of various subpopulations.

There were a total of 27 IDS reports involving at least 71 people since 1996 in IDS. Four reports involved persons who attempted suicide by ingesting aldicarb; one person died. The fourth report concerns the exposure to Tres Pasitos, an aldicarb product sold illegally as a rodenticide in New York City. The exact number of people involved is unclear - possibly as many as 40 people. The majority of the cases were attempted suicide; no deaths were reported.

A total of 15 men were exposed to aldicarb in an occupational setting; 11 cases had symptoms compatible with carbamate poisoning. All were treated at a medical facility; five received specific treatment for cholinesterase inhibition (atropine). All recovered. The majority were not wearing personal protective equipment. All of the cases occurred when workers were loading Temik or cleaning up equipment or an area where the product was stored. Four cases were in minors (ages 14, 15, 17 and 18).

There were three cases involving residential exposure to aldicarb. One of the cases, involved exposure of 20 people to cabbage salad contaminated with aldicarb. In a second case, a man ate berries from a tree that had been illegally treated with Temik. His clinical symptoms are not discussed in the report; however, a urine sample was positive for aldicarb. In the third case, a man used Temik on his yard and vegetable garden. He was diagnosed with "amnesia". No other information on his symptoms, diagnosis or outcome is provided.

The PCC data demonstrate that aldicarb exposure is likely to result in more serious medical outcome and serious medical care than other pesticides. For occupational cases, measures of hazard, such as percentage of cases with moderate or severe outcomes, percentage seen in a health care facility, percentage hospitalized and percentage seen in intensive care unit (ICU) were higher than all other pesticides in the PCC data base. For non-occupational cases involving adults and older children, these measures were increased even more. Patients exposed to aldicarb were ten times more likely to have a life-threatening or fatal outcome and five times more likely to need treatment in an ICU than with all other pesticides. There were too few cases to provide reliable estimates of proportionate hazards to children (less than 6 years of age); however, the pattern of risk in this subpopulation was similar to that seen for non-occupational adults and older children.

A total of 19 articles in the open scientific literature describing intentional or accidental poisonings due to aldicarb exposure were reviewed. Summaries of the articles are included under Literature on Poisonings in this Memorandum. The literature studies provide some limited insight into the questions of: 1) duration of symptoms from aldicarb poisoning; 2) doses at which poisonings occur; and 3) subpopulation sensitivity. Concerning duration of symptoms, there are limited data on the time between onset of symptoms and recovery without specific treatment with atropine. In one study in which people were exposed to cucumbers contaminated with aldicarb, there are data on the duration of illness for 14 people of both sexes, ages 6-54. All of the people had symptoms compatible with carbamate poisoning which

were reported within one hour of exposure, however analysis of the cucumbers for aldicarb was not performed. While the duration of their illnesses was 6 hours or less in 12 of the patients, 2 young girls (ages 7 and 16) were reported to be ill for 12 hours. In an outbreak from Vancouver, Canada involving contaminated cucumbers, it was reported that recovery occurred within two to eight hours. In the report from Louisiana where people ingested cabbage salad, the illness reportedly lasted a median of 4 hours with a range of 1 to 8 hours. It is unknown if the individuals in the last two outbreaks were treated with atropine. In two studies in human volunteers submitted to EPA, subjects recovered within 6 hours but symptoms were relatively mild (sweating and leg weakness). While many references give less than 8 hours as the time to reversal of symptoms after carbamate intoxication, there are data in two young girls that indicate as long as 12 hours may be required.

Concerning doses which produce symptoms of carbamate poisoning, this information was not provided in most of the literature articles. In the report on the cabbage salad ingestion, it was calculated that a 150 lb. adult would have ingested 0.2 mg/kg body weight of aldicarb. In another study, the doses calculated from four outbreaks, in which aldicarb was measured in the food, ranged from 0.0011 to 0.060 mg/kg body weight. In the Canadian cucumber outbreak, it was possible to correlate the quantity of cucumber consumed by an individual with the residue found in the remaining portion of the same cucumbers in only a few cases. Typical symptoms of acute carbamate poisoning were caused by aldicarb residues in the range of 0.01 to 0.03 mg/kg body weight.

Concerning subpopulation sensitivity, several articles have asserted that clinical signs and symptoms of carbamate toxicity can differ in children and adults. Signs and symptoms commonly associated with carbamate poisoning (SLUDGE syndrome) are more commonly observed in adults than in children. This could lead to misdiagnosis and underreporting of carbamate intoxication in children. However, there are no data in the literature which compared the doses at which clinical signs/symptoms occurred in adults versus children that would answer the question about subpopulation sensitivity.

8.0 DATA NEEDS/LABEL REQUIREMENTS

8.1 Toxicology

870.3200

- Comparative Cholinesterase Assay (PND 11 pups and adult rats)
- 1-day dermal toxicity study (including RBC/plasma/brain ChEI measures)
- 1-day inhalation toxicity study (including RBC/plasma/brain ChEI measures)

For aldicarb, the Agency has relied primarily on the non-guideline comparative cholinesterase study in juvenile and adult animals to evaluate the potential sensitivity of young animals to cholinesterase inhibition. However, RBC cholinesterase inhibition was not monitored in that study (whole blood, plasma, and brain). Additionally, there are no comparative cholinesterase activity recovery data available. Since RBC cholinesterase inhibition has been selected as endpoint for derivation for PODs in the aldicarb risk assessment, a comparative cholinesterase assay (PND 11 pups and adult rats) measuring cholinesterase activity (RBC and brain) is required. Time-course data for cholinesterase

should be generated prior to the dose-response study, to determine time to peak effect and time to recover to control values (ChE activity). Protocols should be submitted to OPP for comment prior to study initiation.

Additionally, the previous data gaps of 21-day repeat dermal and repeat dose inhalation studies have been removed and replaced with the requirement for one-day dermal and one-day inhalation studies in which ChE activity (peak effect, time to recovery, dose response) is monitored. These studies will provide more useful data for risk assessment. Protocols should be submitted to OPP for comment prior to study initiation.

8.2 Residue Chemistry

860.1500 Field trials residues in sorghum forage and cotton gin by-products (gin trash). [HED recommends cotton field trials include residues in cottonseed, since the available data for this commodity are limited and are of poor quality.]

Label Changes:

- Registered labels must reflect maximum seasonal use rates (where applicable).
- The restriction against feeding grain sorghum forage must be removed.
- A 10-month plantback interval (PBI) should be specified on EPA Reg. No. 264-331 for crops not listed on the label.

9.0 SUPPORTING DOCUMENTATION

The conclusions from the following supporting documents have been incorporated into the aldicarb preliminary human health risk assessment:

“Aldicarb - Residue and Product Chemistry Chapters of the HED Reregistration Eligibility Decision Document (RED).” [C. Swartz memorandum dated 6/02/00, DP Barcode No. D266396].

“Aldicarb - Update of Incident Data Review of April 10, 1996”
[V. Dobozy memorandum dated 6/24/00, DP Barcode No. D267355].

“Aldicarb Toxicology Chapter for the HED RED,”
[L. Taylor and W. Sette memorandum dated 8/20/02, DP Barcode No. D266321, TXR#: 014220].

“Aldicarb - Revised Dietary Exposure Analyses for the HED Human Health Risk Assessment,”
[F. Fort memorandum dated 10/31/06, DP Barcode No. D299882].

“Aldicarb - Revised Occupational and Residential Exposure Assessment for the Health Effects Division RED,” [J. Dawson memorandum dated 1/11/05, DP Barcode No. D311821].

“Drinking Water Exposure Assessment for Total Aldicarb Residues (Parent, Aldicarb Sulfoxide, and Aldicarb Sulfone) Based on the N-Methyl Carbamate Cumulative Risk Assessment,” [N. Thurman and J. Angier memorandum dated 10/23/06, DP Barcode No. D333309].

“Aldicarb: Acute Dietary Exposure Assessment to Support the Reregistration Eligibility Decision PC Code: 098301,” [S. Nako and J. Xue memorandum dated 11/01/06, DP Barcode No. D299889.]